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(54) Title: DI-SUBSTITUTED NAPHTHYL DERIVATIVES, PREPARATION THEREOF, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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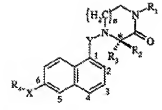

(I)

(a)

(57) Abstract

The invention concerns novel products of general formula (I), their preparation, pharmaceutical compositions containing them and their use for preparing medicines. In general formula (I); R_1 represents a hydrogen atom or an alkyl, aralkyl radical; R_2, R_3 represent a hydrogen atom or an alkyl, aryl, aralkyl, alkythioalkyl, alkysulphonylalkyl, carbamoylalkyl, alkoxyalkyl, hydroxyalkyl radical; R_4 represents -CO-CH(NH_2)-CH_2SH or -CH_2-CH(NH_2)-CH_2SH or (a); X represents an oxygen or nitrogen atom substituted by a radical R_5; Y represents a sulphonyl or carbonyl radical; n is equal to 1 or 2.

(57) **Abrégé**

Nouveaux produits de formule générale (I), leur préparation, les compositions pharmaceutiques qui les contiennent et leur utilisation pour la préparation de médicaments. Dans la formule générale (I), R_1 représente un atome d'hydrogène ou un radical alkyle, aralkyle; R_2, R_3 représentent un atome d'hydrogène ou un radical alkyle, aryle, aralkyle, alkylthioalkyle, alkylsulfonylalkyle, carbamoylalkyle, alkoxyalkyle, hydroxyalkyle; R_4 représente -CO-CH(NH_2)-CH_2SH ou -CH_2-CH(NH_2)-CH_2SH ou (a); X représente un atome d'oxygène ou d'azote substitué par un radical R_5; Y représente un radical sulfonyle ou carbonyle; n est égal à 1 ou 2.

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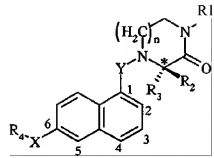
DI-SUBSTITUTED NAPHTHYL DERIVATIVES, PREPARATION THEREOF, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This invention concerns novel derivatives of naphthyl-piperazinone of general formula (I)



(I)

preparation thereof, pharmaceutical compositions containing them and their use for the preparation of medicines.

Farnesyl transferase is an enzyme that catalyses the transfer of the farnesyl group of farnesyl pyrophosphate (FPP) to the terminal cysteine residue of the CAAX tetrapeptidic sequence of a certain number of proteins and in particular p21Ras protein, expressing the *ras* oncogene.

The *ras* oncogene (H-, N- or *K-ras)* is known to play a key role in cellular signalling pathways and the process of cell division. Mutation of the *ras* oncogene or its over-expression is often associated with human cancer: mutated p21Ras protein can be found in many human cancers and in particular in over 50% of colon cancers and 90% of pancreas cancers (Kohl et al., Science, 260,1834-1837,1993).

The inhibition of the farnesyl transferase and consequently of the farnesylation of the p21Ras protein blocks the capacity of the mutated p21Ras protein to induce cell proliferation and to transform normal cells into malignant cells. Furthermore, it has been shown that farnesyl transferase inhibitors are also active on tumoral cell lines that do not express any mutated or over-expressed *ras*, but showing the mutation of an oncogene or the over-expression of an oncoprotein of which the signalling pathway uses the farnesylation of a protein, such as a normal *ras* (Nagasu et al., Cancer Research 55, 5310-5314, 1995; Sepp-Lorenzino et al., Cancer Research 55, 5302-5309,1995).

Inhibitors of Farnesyl transferase are inhibitors of cell proliferation and consequently can be

antitumoral and anti-leukaemia agents.

Di-substituted naphthyl derivatives in position 1.5 or 1.6 have been described respectively in applications WO 95/34535 and WO 97/03050, as presenting enzymatic inhibiting activity of farnesyl transferase, *in vitro,* without however any of these prior compounds described as presenting any satisfactory inhibiting activity at the cell level.

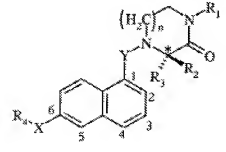
It has now been found, and this is the purpose of this invention, that compounds of general formula (I), due to the substitution on the naphthyl of a piperazinone group, distinct from the compounds of the prior art previously mentioned, show their inhibiting activity at the enzymatic level as well as at the cell level, and this at concentrations that are totally significant.

Due to this activity, compounds of general formula (I) are therefore remarkable antitumoral and anti-leukaemia agents.

Nothing in the prior art suggested carrying out such a modification at the level of the chemical structure and did not indicate the advantageous antineoplastic properties shown by these compounds.

Moreover, according to the invention, the novel products of general formula (I), farnesyl transferase inhibitors, can be competitive with regards to a Farnesyl transferase substrate, such as those described by A.D.Cox and C.J.Der, Biochimica et Biophysica acta, 1333 (1997), f 51-f 71 and in particular p21Ras proteins, such as H-Ras, Ki-Ras, N-Ras, Rho...; with this particularity allowing them to act specifically at the level of the substrate.

This invention concerns the novel compounds of general formula (I)



(I)

in racemic form or of their stereoisomers, as well as in the form of salts.

Products of general formula (I) can posses at least one asymmetric carbon, in particular, when R_2 is different from R_3, this noted as C*: this asymmetric carbon can have the configurations (R) or (S); in particular, products of general formula (I) can have 2 asymmetric carbons, and can therefore occur in the form of 4 stereoisomers: 2 diastereoisomers, and 2 enantiomers, the enantiomers may be in the form of racemic mix.

All of the stereoisomer forms of compounds of general formula (I) are also part of the invention.
In a particularly advantageous manner, C* shows the corresponding configuration in the case where R_2 represents an atom of hydrogen.

In what has been said and in what follows, the expression "stereoisomer", defines the pure form of said stereoisomer or possibly the mixture of "enriched" stereoisomers, i.e. containing primarily said stereoisomer or said form.

In the preceding definitions and in those that follow, and unless otherwise mentioned:

- the alkyl portions and radicals contain 1 to 6 atoms of carbon in a branched or straight chain, and include in particular methyl, ethyl, propyl, butyl, pentyl, hexyl radicals and portions as well as their *iso, sec* and *tert* isomers,
- the term halogen defines the atoms of fluorine, chlorine and bromine, iodine; more preferably, the atoms of chlorine, fluorine;

- the term aryl defining an aromatic hydrocarbon radical of 6 to 10 links, and in the definitions of R_1, R_2, R_3, R_4, unless otherwise mentioned, aryl radicals and aryl portions, like in aralkyl, such as benzyl, may be substituted by an atom of halogen or an alkyl, alkoxy, alkylthio, alkylsulfonyl, cyano, nitro, amino, polyfluoroalkyl radical, such as trifluoroalkyl like trifluoromethyl, perfluoroalkoxy, such as trifluoroalkoxy like trifluoromethoxy; more preferably, the aryl radical or portion represents a phenyl radical, which may be substituted;
- the term BOC defines the tert.butoxycarbonyl radical,
- the term Ph defines the phenyl radical.

In general formula (I):

R_1 represents an atom of hydrogen or an alkyl radical, or an aralkyl radical;

R_2, R_3 identical or different represent independently an atom of hydrogen or a radical chosen from among the alkyl, aryl, alkylthioalkyl, alkylsulfonylalkyl, carbamoylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl radicals of which the aryl portion may be substituted by an atom of halogen;

R_4 represents

$-CO-CH(NH_2)-CH_2SH$, or

$-CH_2-CH(NH_2)-CH_2SH$,

possibly of racemic configuration or that of their stereoisomer, and more particularly the configuration of natural amino acids, where

radicals of formula

X represents either an atom of nitrogen substituted by an R_5 radical, or an atom of oxygen;

R_5 represents an atom of hydrogen or an alkyl, aralkyl, heterocycloalkyl radical;
Y represents a sulfonyl or carbonyl radical;
n is equal to 1 or 2;

Ri_1 represents a heterocyclyl radical which may be substituted,
the term heterocyclyl defining a cyclic radical, saturated or unsaturated, from 5 to 10 links and containing 1, 2, 3 or 4 atoms of nitrogen, and possibly another hetero atom chosen from among the atoms of oxygen or sulphur; said radical can be in particular chosen from among the pyrrolyl, pyrazolyl, imidazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indolizinyl, isoindolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, quinolyl, phtalazinyl, naphtyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, pipridyl, piperazinyl, indolinyl, isoindolinyl, triazolyl, tetrazolyl, thiazolyl, thiazolidinyl, oxazolyl, oxazolinyl, isothiazolyl, isoxazolyl, imidazolyl radicals preferentially; each heterocycle may be substituted on one or more atoms or hetero atoms from which it is composed, by one or several atoms or radicals chosen from among the atoms of halogen, or the alkyl, alkoxy, alkyl, aralkyl, aryl radicals, of which the aryl radicals or portions may themselves be substituted by one or several atoms or radicals, chosen from among the atoms of halogen and/or the alkoxy, cyano, nitro, amino, alkylthio, alkylsulfonyl, polyfluoroalkyl radicals, such as trifluoroalkyl, like trifluoromethyl, polyfluoroalkoxy, such as trifluoroalkoxy, like trifluoromethoxy;

Ri_2 represents an atom of hydrogen, or a radical chosen from among alkyl, aryl or aralkyl, more preferably hydrogen;
in racemic form or their stereoisomers as well as their salts.

Among the compounds of general formula (I), those preferred are those in which:
more preferably R_1 represents an atom of hydrogen;
and/or

more preferably, where R_2 and R_3 each represent an alkyl radical, where one of the substituents R_2 or R_3 represents an atom of hydrogen, and the other of the substituents R_2 or R_3 represents an alkyl, alkylthioalkyl, alkoxyalkyl, aralkyl, hydroxyalkyl radical;

and/or

for R_4, a $-CH_2-CH(NH_2)-CH_2SH$ radical is preferred, preferentially of configuration of the natural amino acid, or a radical

where Ri_1 represents an heterocyclyl radical, more preferably imidazolyl, and may be substituted by one or more atoms or radicals chosen from among the alkyl, aralkyl, benzyl radicals more preferably, of which the aryl part may be substituted by a cyano radical;

Ri_2 represents an atom of hydrogen;

more preferably, X represents an -NH- radical;

more preferably, Y represents a carbonyl radical,

n is equal to 1 more preferably;

in racemic form or their stereoisomers as well as their salts.

Pertaining to compounds that are particularly preferred according to the invention, we shall mention those represented in general formula (I) where:

Ri represents an atom of hydrogen;

and/or

R_2 and R_3 represent or each one an alkyl radical, where one of the substituents R_2 or R_3 represents an atom of hydrogen, and the other of the substituents R_2 or R_3 represents an alkylthioalkyl, hydroxyalkyl radical;

and/or

R_4 represents a $-CH_2-CH(NH_2)-CH_2SH$ radical or a radical

in which Ri_1 represents an imidazolyl radical substituted by an aralkyl radical, more preferentially benzyl, of which the aryl part is substituted by a cyano radical;

Ri_2 represents an atom of hydrogen;

R_4 represents more preferably a radical

and/or

X represents a -NH- radical;

and/or

Y represents a carbonyl radical,

and/or

n is equal to 1

in racemic form or their stereoisomers as well as their salts.

For the purposes of illustration and in a way that does not limit the claimed compounds, especially any compound of general formula (I) can be mentioned, selected individually from among:

4- [6- (2 (R) -amino- 3-mercapto-propylamino) -1 -naphthyl-carbonyl] -3 (S) - (2-methylthio-ethyl)-2-oxo-piperazine

4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-benzyl-2-oxo-piperazine

4- [6- (2 (R)-amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl]-3 (S) -hydroxy-methyl-2-oxo-piperazine

4- [6- (2 (R) -amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -3 (S) -butyl-2-oxo-piperazine

4- [6- (2 (R) -amino-3-mercapto-propylamino)-1 -naphthyl-carbonyl] -3 (R,S) -methoxymethyl-2-oxo-piperazine

3 (S) -butyl-4- {6- [1 - (4-cyanobenzyl) - 1H-imidazol-5-yl-methylamino] -1 -naphthyl-carbonyl} -2-oxo-piperazine

4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-methyl-2-oxo-piperazine

4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine

4- [6- (2 (R) -amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -1 -methyl-3 (S) -methylthioethyl-2-oxo-piperazine

4- [6- (2 (R) -amino-3 -mercapto-propylamino) -1 -naphthyl-carbonyl] -1 -benzyl-3 (S) -methylthioethyl-2-oxo-piperazine

4-[6-(1-methyl-1H-imidazol-5-yl-methylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl) -2-oxo-piperazine

3(S)-(2-carbamoyl-ethyl)-4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine

4- [6- (3-pyridyl-methylamino) -1 -naphthyl-carbonyl] -3 (S) - (2-methylthio-ethyl) -2-oxo-piperazine

4- {6- [1 - (4-cyanobenzyl) - 1H-imidazol-5-yl-methylamino] -1 -naphthyl-carbonyl} -] -3 (S) -(2-methylthio-ethyl)-2-oxo-piperazine

4-{6-[1-(4-cyanobenzyl)-1H-imidazol-5-yl-methylamino]-1-naphthyl-carbonyl}-]-3(S)-hydroxymethyl-2-oxo-piperazine

or their other stereoisomers, possibly in racemic form as well as their salts.

More preferentially, it can again be mentioned according to the invention, any compound of general formula (I) selected individually from among:
4- [6- (2 (R) -amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] - 3 (S) - (2-methylthio-ethyl)-2-oxo-piperazine

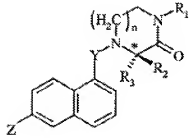
4- {6- [1 - (4-cyanobenzy 1) -1 H-imidazol-5-yl-methylamino] -1 -naphthyl-carbonyl} -] -3 (S) -(2-methylthio-ethyl) -2-oxo-piperazine

4- {6- [1 - (4-cyanobenzy 1) -1 H-imidazol-5-yl-methylamino] -1 -naphthyl-carbonyl} -]-3 (S) - hydroxymethyl-2-oxo-piperazine

or their other stereoisomers, possibly in racemic form as well as their salts.

This invention also concerns the preparation of novel products of general formula (I). Various operating protocols as well as reactive intermediaries likely to be used in order to prepare compounds of general formula (I) are proposed. Of course, included in this invention, are analogue methods aiming to lead to these same compounds: this is part of the general knowledge of those skilled in the art to apply or adapt these methods in order to implement the invention.

According to this invention, products of general formula (I) where R_1, R_2, R_3, R_4, Y and n are defined as such in general formula (I) and X represents an atom of nitrogen substituted by R_5=H, can be obtained using the product of general formula (II)



(II)

where R_1, R_2, R_3, Y and n are defined as such in general formula (I) and Z represents an amino radical, possibly in the form of a mixture of diastereoisomers and/or enantiomers, or in the form of pure diastereoisomers or enantiomers.

♦ either, when R_4 represents the radical -CO-CH(NH_2)-CH_2SH,

by action of a protected amino acid of general formula

$$HO_2C\text{-}CH(NHG_1)\text{-}CH_2SG_2 \qquad (III)$$

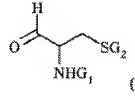
where G_1 represents a protective group of an amino function such as a benzyloxycarbonyl, tert.butoxycarbonyl or vinyloxycarbonyl radical, and G_2 represents a protective group of a mercapto function such as trithyl (-CPh_3).

Advantageously, according to the invention, G_1 represents a BOC radical and G_2 represents a trityl radical (-CPh_3).

Generally, this reaction is carried out by coupling of the appropriately protected amino acid, for example in the presence of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium, hexafluorophosphate (HBTU), N-hydroxybenzo-triazole (HOBT) and diisopropylethylamine in an organic solvent for example made up of a mixture of N-methylpyrrolidone (NMP) and dimethylformamide (DMF), followed by a deprotection reaction of the protective groups of the amino and mercapto groups.

♦ or when R_4 represents the radical -CH_2-CH(NH_2)-CH_2SH,

by action of a reagent of general formula

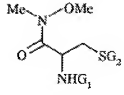


(IV),

where G_1 and G_2 are defined as previously, followed by a deprotection reaction of the amino and mercapto radicals by cleavage of protective groups G_1 and G_2.

Generally, the reaction of the product of general formula (IV) on the product of general formula (II) is carried out under conditions of reductive amination, especially by working for example in an organic solvent such as acetonitrile, in the presence of acid such as acetic acid, possibly on a 3 Å molecular sieve, then by the action of a reducing compound, such as sodium cyanoborohydride ($NaBH_3CN$) or sodium triacetoxyborohydride ($NaBH(OCOCH_3)_3$) or the

BH_3.pyridine complex, by working in an organic solvent such as ethyl alcohol, at a temperature more preferably between 0°C and the reflux temperature of the solvent. The product of general formula (IV) can be obtained using the product of the general formula



where G_1 and G_2 are defined as previously, according to the method described in patent application EP 0 618 221.

Generally, the deprotection reaction of the amino and thiol radicals by cleavage of the G_1 and G_2 groups takes place by adaptation or analogy of known deprotection methods described by T.W.Greene, Protective groups in organic chemistry, Wiley-interscience (1991); it is particularly preferred to work in an organic solvent such as a halogenated aliphatic hydrocarbon such as methylene chloride, in the presence of trifluoroacetic acid (TFA) and possibly triethylsilane and more preferably at an ambient temperature,

♦ where R_4 represents a radical of formula

where Ri_1 and Ri_2 are such as defined in general formula (I), by action of a reagent of general formula

(V)

where Ri_1 and Ri_2 are defined as previously.

The reaction of the product of general formula (V) on the product of general formula (II) is carried out under conditions of reductive amination: generally, by working

in an organic solvent such as acetonitrile, in the presence of acid such as acetic acid, possibly on a 3 Å molecular sieve, then by the action of a reducing compound, such as sodium cyanoborohydride ($NaBH_3CN$) or sodium triacetoxyborohydride ($NaBH(OCOCH_3)_3$), or the BH_3.pyridine complex by working for example in an organic solvent such as ethyl alcohol, at a temperature more preferably between 0°C and the reflux temperature of the solvent.

Products of general formula (V) can be obtained commercially or through functionalisation of carboxaldehydes available commercially according to the methods described by Larock, Comprehensive Organic Transformations, VCH, New York, 1989, or according to the procedures described in the examples, or according to the methods described by J.Jeong Lee J.Heterocyclic Chem., (1998), *35,* 81-89, by Sebti J.Med.Chem, (1996), *39,* 219, or by G.Bold, J.Med.Chem, (1998), *41,* 3387-3401.

Products of general formula (I) where R_1, R_2, R_3, R_4, Y and n are defined as such in general formula (I) and X represents an atom of nitrogen substituted by R_5 representing an alkyl, aralkyl or heterocycloalkyl radical, can be obtained using products of general formula (I) where R_1, R_2, R_3, R_4, Y and n are defined as such in general formula (I) and X represents an atom of nitrogen substituted by R_5=H by alkylation with R_5-Hal, where R_5 represents an alkyl, aralkyl or heterocycloalkyl radical, and Hal represents an atom of halogen, by working for example in the presence of a base, in particular a mineral base such as potassium carbonate, in an organic solvent such as acetonitrile, and more preferably at an ambient temperature.

Products of general formula (I) obtained as a result of the method according to the invention can have different stereoisomer, enantiomer and/or diastereoisomer forms, which can be separated by traditional separation methods, such as chromatography or crystallisation. For diastereoisomers, more preferably high-performance liquid chromatography on silica column is used (normal phase, reversed phase C_{18}, or chiral phase, in particular for enantiomers chromatography on chiral column, such as that of the Pirkle type

(Pirkle and coll., Asymetric Synthesis, vol.1, Academic Press (1983)), or through synthesis using chiral precursors. The same applies to products of general formula (II) where R_1, R_2, R_3, Y and n are defined as such in general formula (I) and Z represents an amino radical, with subsequent synthesis steps able to be carried out using separated and purified isomers (enentiomers, diastereoisomers).

Products of general formula (II) where R_1, R_2, R_3, Y and n are defined as such in general formula (I) and Z represents an amino radical can be obtained using corresponding products of general formula (II) where R_1, R_2, R_3, Y and n are defined as such in general formula (I) and Z represents a nitro radical, for example by catalytic reduction, in a hydrogen atmosphere, in particular using palladium on carbon, by working for example in an organic solvent, such as an alcohol, such as ethyl alcohol, at a temperature more preferably between 20°C and the temperature of ebullition of the solvent, or using tin tetrachloride, by working in an organic solvent, such as an alcohol, such as ethyl alcohol.

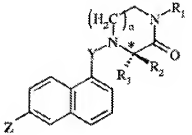
Products of general formula (II) where R_1, R_2, R_3 and n are defined as such in general formula (I), Z represents an amino radical and Y represents an $-SO_2$ radical can be obtained using corresponding products of general formula (II), where R_1, R_2, R_3, and n are defined as such in general formula (I), Y represents an $-SO_2$ radical and Z represents a protected amino radical -NHG, G representing a protective group of the amino function, such as BOC, -COalkyl, such as $-COCH_3$, $-COCF_3$, by working par adaptation or application of known deprotection methods described by T.W.Greene, Protective groups in organic chemistry, Wiley-interscience (1991).

This reaction may be followed by a separation step of the isomers, diastereoisomers and or enantiomers, according to the methods described above.

Products of general formula (I) where R_2, R_3, R_4, Y and n are defined as such in general formula (I), X represents an atom of oxygen and R_1 represents an atom of hydrogen or an alkyl or aralkyl radical, can be obtained using corresponding compounds of general formula (II) where R_2, R_3, Y and n are

such as defined as previously, Z presents a -OR_4, R_4 radical being defined as previously, and R_1 represents an atom of hydrogen for example by action of a base, such as an alkaline metal hydride, sodium hydride for example, followed possibly by the reaction of alkylation of the atom of nitrogen with R_1-Hal, where R_1 represents an alkyl or aralkyl radical. It is possible to proceed in the same manner, in order to obtain products of general formula (II) where R_2, R_3, Y and n are defined as previously, Z represents a nitro radical and R_1 represents an alkyl or aralkyl radical, using compounds of general formula (II) where R_2, R_3, Y and n are such as defined previously, R_1 represents an atom of hydrogen and Z represents a nitro radical.

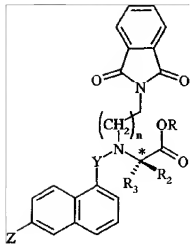
Compounds of general formula (II) are also part of this invention,



(II)

where R_1, R_2, R_3, Y and n are defined as such in general formula (I) and Z represents a nitro, amino, possibly protected, radical, or -OR_4 with R_4 defined as in general formula (I).

Compounds of general formula (II) where R_2, R_3, Y and n are such as defined as previously, Z represents an -OR_4 radical with R_4 defined as previously, or a nitro radical, or a protected amino radical and R_1 represents an atom of hydrogen can be obtained using compounds of general formula (VI)

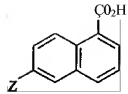


(VI)

where R_2, R_3, Y and n are such as defined as previously, Z represents an $-OR_4$ radical or a nitro radical or a protected amino radical and R represents an alkyl radical, such as methyl, for example through the action of an amino base such as hydrazine, by working in an organic solvent such as an alcohol, such as ethyl alcohol, at temperatures more preferably between 10°C and the temperature of ebullition of the solvent, more preferably at a temperature of approximately 20°C.

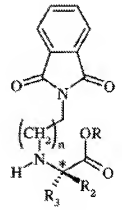
Products of general formula (VI) where R_2, R_3, Y, R and n are such as defined as previously, and Z represents an $-OR_4$ radical, R_4 being defined as previously, can be obtained using products of general formula (VI) where R_2, R_3, Y, R and n are such as defined as previously, and Z represents a -OH radical through exchange reaction of the atom of hydrogen with an $-R_4$ radical, using compounds of general formula Hal-R_4, where R_4 is defined as previously and Hal represents an atom of halogen, advantageously chlorine or bromine, in the presence for example of a mineral base, such as an alkaline metal hydride, especially sodium hydride by working at temperatures more preferably between 0°C and the ebullition temperature of the solvent.

Products of general formula (VI) where R_2, R_3, R and n are such as defined as previously, Y represents a carbonyl radical and Z represents an -OH radical or a nitro radical that can be obtained using compounds of general formula (VII)



(VII)

where Z is defined as previously, by action of compounds of general formula (VIII)

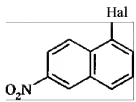


(VIII)

where R_1, R_2, R_3 and n are defined as previously.

Generally, this reaction is carried out using an activated form of acids of general formula (VII), prepared in situ or not, such as a halide, chloride more preferably, or a mixed or symmetric anhydride. Advantageously, work using oxalyl chloride, in the presence of an organic or mineral base, more preferably an amino base, such as triethylamine in an organic solvent, more preferably a halogen solvent such as methylene chloride, at temperatures more preferably between 10°C and the temperature of ebullition of the solvent.

Compounds of general formula (VII) can be obtained commercially when Z represents a hydroxy radical, or when Z represents a nitro radical using compounds of general formula (IX)



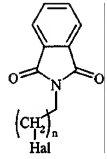
(IX)

where Z is defined as previously and Hal represents an atom of halogen, more preferably an atom of bromine, by application or adaptation of known carboxylation reactions.

Advantageously, this reaction can be carried out by action of carbon monoxide, in the presence of a catalyst, for example palladium acetate, in the presence of ligands of the palladium, such as trialkylphosphines, like triphenylphosphine, in the presence of bases, such as sodium acetate, and possibly in the presence of alkaline metal iodide, such as potassium iodide. This reaction takes place in an organic solvent, such as dimethylformamide, possibly in the presence of water, at a temperature more preferably between 0°C and the temperature of ebullition of the solvent.

Compounds of general formula (IX) can be obtained according to the J.Braun et coll. method, Ber.55, 1687 (1922).

Compounds of general formula (VIII) where R_1, R_2, R_3 and n are defined as previously can be prepared using compounds of general formula (X)



(X)

where n is defined as previously and Hal represents an atom of halogen, more preferentially chlorine or bromine, through the action of amino acid derivatives of general formula (XI)

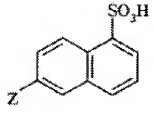
(XI)

where R_1, R_2 and R_3 are defined as previously; this action may be carried out by working for example using an organic or mineral base, such as potassium carbonate, possibly in the presence of an alkaline metal halide, more preferably potassium iodide, in an organic solvent such as acetonitrile, at temperatures more preferably between 0°C and the temperature of ebullition of the solvent.

Phtalimide derivatives of general formula (X) and amino acid derivatives of general formula (XI) can be obtained commercially or possibly through functionalisation of phtalimides or amino acids available commercially or according to the methods described in the examples, for example by using the procedures described by S.Sagan, Biorg.Med.Chem.Letters (1996), 4, 2167-2178, by W.Oppolzer Helv.Chim.Acta, (1994), 77, 2366-2380 or according to the methods described by Larock, Comprehensive Organic Transformations, VCH, New York, 1989.

More preferably, it is preferable to use an amino acid of natural series, being understood that the configuration of the amino acid can be modified during the coupling reaction and that several stereoisomers can be obtained resulting from this reaction.

Products of general formula (VI) where R_2, R_3, R and n are such as defined as previously, Y represents a sulfonyl radical and Z represents a nitro or protected amino radical can be obtained using compounds of general formula (XII)



(XII)

where Z is defined as previously, through the action of compounds of general formula (VIII) where R, R_2, R_3 and n are defined as previously. Generally, this reaction is carried out using an activated form of acids of general formula (XII), possibly prepared in situ, such as a halide, chloride more preferably. Advantageously, thionyl chloride or chlorosulfonic acid are used, followed by the action of the amine (VIII) within an organic solvent

such as pyridine or methylene chloride, at a temperature more preferably between 0°C and the ebullition temperature of the solvent.

Compounds of general formula (XII) can be of commercial nature, when Z represents a nitro radical, or

when Z represents a protected amino radical, they can be prepared using products of general formula (XII) in which Z represents an amino radical, through protection of the amino function, by working through the application or adaptation of protective methods of functional groups described previously.

The reaction mixtures obtained by the various methods described previously are treated according to traditional physical (evaporation, extraction, distillation, chromatographic, crystallisation for example) or chemical (formation of salts for example) methods.

Compounds of formula (I) may be transformed into addition salts with an organic or mineral acid through the action of such an acid within an organic solvent such as an alcohol, a ketone, an ether or a chlorinated solvent. These salts are also part of the invention; advantageously, products of general formula (I) according to the invention can occur in the form of trifluoroacetate.

This invention also concerns any pharmaceutical composition containing at least one product of general formula (I) in association with one or more pharmaceutically acceptable diluents or additives, whether inert or biologically active.

The novel products of general formula (I) can occur in the form of non-toxic and pharmaceutically acceptable salts. Examples of pharmaceutically acceptable salts are addition salts with organic or mineral acids such as acetate, propionate, succinate, benzoate, fumarate, maleate, methane sulfonate, isethionate, theophyllinacetate, salicylate, methylene-bis-b-oxynaphtoate, chlorhydrate, sulfate, nitrate and phosphate.

This invention concerns the use of compounds of general formula (I) for the preparation of pharmaceutical compositions useful in the treatment and/or prevention of pathological conditions pertaining cellular signalling pathways, associated with farnesyl transferase, or with their consequences or symptoms.

This invention also concerns the use of compounds of general formula (I) according to the invention for the preparation of pharmaceutical compositions useful for inhibiting farnesyl transferase, and more especially for inhibiting farnesylation of Ras proteins produced by the *ras* oncogenes.

In particular, this invention concerns the use of compounds of general formula (I) according to the invention for the preparation of pharmaceutical compositions useful for the treatment of diseases pertaining to cellular proliferations through the inhibition of farnesyl transferase and in particular for the treatment of diseases pertaining to cellular proliferations, over-expressing any one of the H-Ras, N-Ras or K-Ras oncoproteins, or having a mutation of any one of the corresponding *ras* oncogenes.

The invention concerns in particular the use of compounds of general formula (I) according to the invention for the preparation of pharmaceutical compositions useful for the treatment of diseases pertaining to cellular proliferations, malignant or benign, of cells of various tissues and/or organs, including muscular, bone or connective tissue, skin, brain, lungs, sexual organs, lymphatic or renal systems, mammary or blood cells, liver, digestive system, colon, pancreas and thyroid or adrenaline glands, and including the following pathologies: psoriasis, restenosis, solid tumours, Kaposi's sarcoma, carcinomas, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanomas, teratocarcinomas, gliomas, multiple myelomas, chronic lymphatic leukaemias, chronic or acute granulo-cyte lymphomas, and cancers such as cancer of the pancreas, colon, lung, ovary, breast, brain, prostate, liver, stomach, bladder or testicles.

The invention concerns very especially the use of compounds of general formula (I) according to the invention for the preparation of pharmaceutical compositions useful for the treatment of cancers such as cancer of the pancreas, colon, lung, ovary, breast, brain, prostate, liver, stomach, bladder or testicles, and more advantageously cancer of the colon and pancreas, especially the colon.
Said treatment can in particular be carried out by inhibition of tumour growth, especially through the inhibition of farnesyl transferase, or through inhibition of the tumour growth expressing the activated *ras* oncogene.

Another purpose of this invention is any association of a product of general formula (I) with one or more pharmacologically active and compatible compounds and/or radiotherapy treatment; said compounds being preferentially active principles known for their inhibiting activity of cell proliferation and especially for their activity in treating cancer; they can be preferentially antiproliferative compounds acting in any one of the stages of the signalling pathway of the *ras* oncogene as a protein tyrosine kinase inhibitor, or another inhibitor of farnesyl transferase, or an HMG-Co-reductase inhibitor, or cytotoxic compounds normally used in treating cancer, or gene therapy treatment resulting for example from the administration of an antioncogene.

In particular, other therapeutic treatment and/or products that can be used in association with products of general formula (I) can be chosen from among antineoplastic medicines, monoclonal antibodies, immunologic therapies or radiotherapies or biological response modifiers. The response modifiers include, but are not limited to, lymphokines and cytokines such as interleukins, interferons (α, ß or δ) and TNF. Other chemotherapeutic agents useful in treating disorders caused by abnormal cell proliferation include, but are not limited to, aldylating agents such as nitrogen mustards like mechloretamine, cyclophosphamide, melphalanum and chlorambucil, alkyl sulphonates such as busulfan, nitrosyl-ureas such as carmustine, lomustine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues like methotrexate, pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products such as vinca-alcaloids such as vinblastine, vincristine and vendesine, taxoid derivatives, topoisomerase inhibitors such as camptothecine derivatives, podophyllotoxins like etoposide and teniposide, antibiotics like dactinomycin, daunorubicin, doxorubicine, bleomycin, plicamycin and mitomycine, enzymes such as L-

asparaginase, various agents such as platinum coordination complexes such as cisplatin, substituted ureas such as hydroxyurea, methylhydrazine derivatives like procarbazine, adreno-cortical suppressors like mitotane and aminoglutethymide, hormones and antagonists such as adrenocorticosteroids like prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, estrogens such as diethylstilbestrol and ethynylestradiol, anti-estrogens such as tamoxifen, androgens such as testosterone propionate and fluoxymesterone.

The products according to the invention can be used to prevent or delay the appearance or reappearance of pathological conditions or to treat these pathological conditions.

The products according to the invention can be administered by mouth, parenterally or intraperitoneally or rectally, more preferably by mouth.
Compositions for administration by mouth include caplets, pills, powders or granules. In these compositions the active product according to the invention is mixed with one or more inert diluents such as saccharose, lactose or starch. These compositions can include substances other than diluents, for example a lubricant such as magnesium stearate.

As liquid compositions for administration by mouth, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs containing inert diluents such as water or medicinal oil can be used. These compositions may also include substances other than diluents, for example wetting, sweetening or flavouring agents.

Compositions according to the invention for administration parenterally can be sterile aqueous or non-aqueous solutions, suspensions or emulsions. As solvent or excipient, propyleneglycol, a polyethylene glycol, vegetable oils, especially olive oil or injectable organic esters for example ethyl oleate can be used. These compositions may also contain additives, especially wetting agents, emulsifiers and dispersants. Sterilisation can be carried out in several ways, for example using a bacteriological filter, by incorporating into the composition sterilant agents or by heating. They may also be prepared in the form of solid sterile compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

Compositions for rectal administration are suppositories which may contain, other than the active ingredient, excipients such as cocoa butter.

The doses used in order to implement the methods according to the invention are those that allow prophylactic treatment or a maximum therapeutic response. Doses vary according to the form of administration, the particular product selected and the characteristics proper to the subject to be treated. In general, the doses are those which are therapeutically effective for the treatment of disorders caused by abnormal cell proliferation, and especially cytostatic treatment. The products according to the invention can be administered as frequently and as long as necessary in order to obtain the desired therapeutic effect.

Generally, doses are, in humans, between 0.1 and 10000 mg/kg per day, preferentially between 100 and 2000 mg/kg per day, more preferably by mouth. It is understood that, in order to choose the most appropriate dosage,

the method of administration, weight of the patient, his general health status, age and any factors that can have an influence of the effectiveness of the treatment must be taken into account.

Generally, the doctor shall determine the appropriate dosage according to age, weight and all other factors proper to the subject to be treated.

Example 17 illustrates compositions according to the invention.

The following examples are presented for the purposes of illustration and do not limit this invention.

EXAMPLE 1: Preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine

The 1-bromo-6-nitro-naphtalène is prepared according to the BRAUN, J and coll. method, Ber., 55,1687,1922.

To a solution composed of 21.4 g of 1-bromo-6-nitro-naphtalène in 425 cm3 of dimethylformamide and 3 cm3 of water, is added 33.3 g of potassium acetate, 14.1 g of potassium iodide, 4.45 g of triphenylphosphine then 1.9 g of palladium diacetate. The reaction mixture is stirred in a carbon monoxide atmosphere for 6 hours at a temperature of approximately 130°C, then concentrated under reduced pressure. The residue is taken up in 450 cm3 of water and 200 cm3 of ethyl acetate, alkalised with 30 cm3 of aqueous solution 10 N of sodium hydroxide, then filtered on glass frit lined with celite. The aqueous phase is washed two times with 150 cm3 of ethyl acetate, acidified with 85 cm3 of aqueous solution 11.8 N of hydrochloric acid, then extracted three times with 150 cm3 of ethyl acetate. The organic phases are washed two times with 100 cm3 of water, dried on magnesium sulphate, filtered then concentrated under reduced pressure. The residue is taken up by 100 cm3 of pentane, spun and dried. 15.8 g (85%) of 6-nitro-naphtalène-1-carboxylique acid is obtained in the form of a beige solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 7.81 (t, J = 8 Hz, 1H: H3 of the naphthyl); from 8.30 to 8.45 (mt, 1H: H8

of the naphthyl); from 8.30 to 8.45 and 8.52 (respectively mt and d, J = 8 Hz, 1H each: H4 and H2 of the naphthyl); from 9.00 to 9.15 (mt, 2H: H7 and H5 of the naphthyl); from 13.05 to 13.65 (mf spread, 1H: COOH).

To a solution composed of 10 g of methyl ester chlorhydrate of the L-methionine in 250 cm3 of acetonitrile, 13.1 g of N-(2-bromoéthyl)-phtalimide, 8.3 g of potassium iodide and 26.5 g of potassium carbonate are added. The reaction mixture is stirred for 48 hours with the acetonitrile reflux. The suspension is filtered, then the filtrate is concentrated under reduced pressure. The residue is purified by silica chromatography by eluting with a methylene chloride-ethyl acetate mixture (7-3 in volume). 7.4 g (44%) of methyl ester of the N-(2-phtalimido-ethyl)-L-methionine are obtained in the form of a white powder for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): from 1.55 to 1.85 (mt, 2H: CH_2 of the methyl-thio-ethyl); 1.95 (s, 3H: SCH_3); 2.29 (mf, 1H: NH); 2.42 (t, J = 7.5 Hz, 2H: CH_2S); 2.60 and 2.84 (2 mts, 1H each: CH_2N); from 3.25 to 3.40 (mt: 1H corresponding to the NCHCO); from 3.50 to 3.75 (mt, 2H: CH_2-phtalimido); 3.62 (s, 3H: $COOCH_3$); from 7.80 to 7.95 (mt, 4H: H aromatics of the phtalimido).

To a solution composed of 2.17 g of 6-nitro-naphtalène-1-carboxylique acid in 100 cm3 of methylene chloride, 1.33 cm3 of oxalyl chloride is added, then 0.1 cm3 of dimethylformamide. The reaction mixture is stirred for 2 hours at a temperature of approximately 20°C, then concentrated under reduced pressure. The residue is placed in solution in 50 cm3 of tetrahydrofuran, and added to a solution made up of 3.36 g of methyl ester of the N-(2-phtalimido-ethyl)-L-methionine and 2.8 cm3 of triethylamine in 100 cm3 of tetrahydrofuran. The reaction mixture is stirred for 48 hours at a temperature of approximately 20°C. The solution is filtered, then concentrated under reduced pressure. The residue is purified par silica chromatography by eluting with a methylene chloride-ethyl acetate mixture (9-1 in volume). 4 g (74%) of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-methionine are obtained in the form of a yellow oil for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 393 K, δ in ppm): from 1.90 to 2.80 (mt, 4H: 2 CH_2 of the methyl-thio-ethyl); 2.09 (s large, 3H: SCH_3); from 3.45 to 4.00 (mt, 4H: phtalimidoCH_2CH_2NCO); 3.70 (s, 3H: COOCH3); 4.56 (mf, 1H: NCHCO); from 7.60 to 8.15 (mt, 7H: H3 - H4 - H8 of the naphthyl and H aromatics of the phtalimido); 8.15 (d large, J = 9 Hz, 1H: H7 of the naphthyl); 8.29 (d, J = 8 Hz, 1H: H2 of the naphthyl); 8.89 (s large, 1H: H5 of the naphthyl).

To a solution composed of 2.9 g of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-methionine in 92cm3 of ethyl alcohol, 2.6 cm3 of hydrazine hydrate are added. The reaction mixture is stirred for 72 hours at a temperature of approximately 20°C, then concentrated under reduced pressure. The residue is placed in solution in 150 cm3 of methylene chloride and washed two times with 100 cm3 of water. The solution is filtered, dried on magnesium sulphate, then dry concentrated under reduced pressure. 1.1 g (49%) of 3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine are obtained in the form of a beige solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 393 K, δ in ppm): from 2.00 to 2.40 (mt, 2H: CH_2 of the methyl-thio-ethyl); 2.08 (s large: the 3H corresponding to the SCH_3); from 2.55 to 2.80 (mt, 2H: CH_2S); from 3.05 to 3.50 (mt: the H corresponding to the $CONCH_2CH_2NCO$); 7.66 (mf, 1H: CONH); from 7.75 to 7.85 (mt, 2H: H3 and H4 of the naphthyl); 8.03 (d, J = 9 Hz, 1H: H8 of the naphthyl); 8.29 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 8.36 (mt, 1H: H2 of the naphthyl); 9.00 (d, J = 2 Hz, 1H: H5 of the naphthyl).

To a solution composed of 1.1 g of 3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine in 6 cm3 of ethyl alcohol and 22 cm3 of ethyl acetate, 3.2 g of stannous chloride dihydrate (II) are added. The reaction mixture is stirred for 1.5 hours at a temperature of approximately 70°C, poured over 45 cm3 of water then brought to a pH close to 7 by adding a 5% aqueous solution of sodium acid carbonate. The mixture obtained is filtered on glass frit lined with celite. The solution is extracted two times with 25 cm3 of ethyl acetate. The organic phases are dried on magnesium sulphate, filtered and dry concentrated under reduced pressure. 0.99 g (quantitative yield) of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine are obtained in the form of a beige solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 393 K, δ in ppm): from 2.00 to 2.35 (mt, 2H: CH_2 of the methyl-thio-ethyl); 2.08 (mf, 3H: SCH_3); from 2.55 to 2.75 (mt, 2H: CH_2S); from 3.10 to 3.40 (mt: the H corresponding to the $CONCH_2CH_2NCO$); from 4.40 to 5.20 (mf highly spread: 1H corresponding to the NCHCO); 5.15 (s large, 2H: NH_2); 6.96 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.00 to 7.10 (mt, 2H: H4 and H7 of the naphthyl); 7.34 (t, J = 8 Hz, 1H: H3 of the naphthyl); 7.49 (d, J = 9 Hz, 1H: H8 of the naphthyl); from 7.55 to 7.65 (mt, 1H: CONH); 7.59 (d, J = 8 Hz, 1H: H2 of the naphthyl).

To a solution composed of 0.99 g of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine in 100 cm3 of methylene chloride, 2.6 g of S-triphenylmethyl-N-tert-butoxycarbonyl-L-cysteinal and molecular sieve (4Å) are added. The reaction mixture is stirred for 3 hours at a temperature of approximately 20°C, then 1.7 g of sodium triacetoxy-borohydride are added. The reaction mixture is stirred for 72 hours at a temperature of approximately 20°C, filtered, then concentrated under reduced pressure. The residue is purified by silica chromatography by eluting with a methylene chloride-ethyl acetate mixture (9-1 in volume), then with methanol. 0.8 g (30%) of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine are obtained in the form of a beige solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 393 K, δ in ppm): 1.38 (s, 9H: $OC(CH_3)_3$); from 2.00 to 2.75 (mt, 6H: the 2 CH_2S and CH_2 of the methyl-thio-ethyl); 2.06 (s large: the 3H corresponding to the SCH_3); from 3.05 to 3.45

(mt, 6H: $CONCH_2CH_2NCO$ and CH_2N of the propylamine); 3.74 (mt, 1H: CHN of the propylamine); from 4.60 to 5.05 (mf highly spread: 1H corresponding to the NCHCO); 6.80 (s large, 1H: H5 of the naphthyl); 6.96 (d large, J = 9 Hz, 1H: H7 of the naphthyl); from 7.00 to 7.40 (mt, 17H: H aromatics of the triphenylmethyl - H3 and H4 of the naphthyl); from 7.45 to 7.65 (mt, 2H: H2 and H8 of the naphthyl).

To a solution composed of 0.5 g of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S) - (2-methylthio-ethyl) -2-oxo-piperazine in 4 cm3 of methylene chloride and 0.15 cm3 of triethylsilane, 4 cm3 of trifluoroacetic acid are added. The reaction mixture is stirred for 1 hour at a temperature of approximately 20°C, then concentrated under reduced pressure. The residue is triturated two times with 5 cm3 of pentane, two times with 5 cm3 of hexane, two times with 5 cm3 of ethyl ether, then dried under reduced pressure. The residue is purified via high-performance liquid chromatography (phase C18) by eluting with an acetonitrile-water mixture containing 0.07% of trifluoroacetic acid. After freeze-drying, 0.1 g (15%) of trifluoroacetate of 4-[6-(2(R)-amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -3 (S) - (2-methylthio-ethyl) -2-oxo-piperazine are obtained in the form of a beige powder for which the characteristics are as follows:

- magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 393 K, δ in ppm): from 1.95 to 2.30 (mt, 2H: CH_2 of the methyl-thio-ethyl); 2.07 (mf, 3H: SCH_3); from 2.50 to 2.75 (mt, 2H: CH_2S of the methyl-thio-ethyl); from 2.75 to 3.45 (mt: the 6H corresponding to the $CONCH_2CH_2NCO$ and CH_2S); from 3.50 to 3.65 (mt, 2H: CH_2N of the propylamine); 3.72 (mt, 1H: CHN of the propylamine); from 4.55 to 5.15 (mf highly spread: 1H corresponding to the NCHCO); 6.97 (d, J = 2 Hz, 1H: H5 of the naphthyl); 7.11 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.15 (d, J = 8 Hz, 1H: H4 of the naphthyl); 7.40 (t, J = 8 Hz, 1H: H3 of the naphthyl); 7.57 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.63 (mf, 1H: CONH); 7.68 (d, J = 8 Hz, 1H: H2 of the naphthyl).

-ultimate analysis: $C_{21}H_{28}N_4O_2S_2,1.8\ CF_3CO_2H$

Calculated (%): C = 46.32; H = 4.71; N = 8.78; S = 10.05

Found (%): C = 46.52; H = 4.51; N = 8.73; S = 9.80

EXAMPLE 2: Preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-benzyl-2-oxo-piperazine

By proceeding as in example 1 for the preparation of methyl ester of the N-(2-phtalimido-ethyl)-L-methionine, but using 10 g of the methyl ester chlorhydrate of the L-phenylalanine, 3.5 g (20%) of methyl ester of the N-(2-phtalimido-ethyl)-L-phenylalanine are obtained in the form of a colourless oil for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 2.26 (mt, 1H: NH); 2.65 and from 2.70 to 2.90 (2 mts, 1H each: CH_2N); 2.78 (d, J = 6.5 Hz, 2H: $ArCH_2$); from 3.40 to 3.75 (mt, 3H: CH_2-phtalimido and NCHCO); 3.53 (s, 3H: $COOCH_3$); from 7.05 to 7.25 (mt, 5H: H aromatics of the phenyl); from 7.80 to 7.95 (mt, 4H: H aromatics of the phtalimido).

By proceeding as in example 1 for the preparation of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-methionine, but using 3.5 g of methyl ester of the N-(2-phtalimido-ethyl)-L-phenylalanine, 3.9 g (70%) of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-phenylalanine are obtained in the form of a yellow solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 393 K, δ in ppm): from 3.15 to 3.30 and 3.42 (respectively mt and dd, J = 14 and 6 Hz: the 2H corresponding to the CH_2Ar); from 3.30 to 3.85 (mf: the 4H corresponding to the phtalimidoCH_2CH_2NCO); 3.69 (s, 3H: $COOCH_3$); 4.67 (dd, J = 9 and 6 Hz, 1H: NCHCO); from 7.05 to 7.50 (mt: the 5H corresponding to the H aromatics of the phenyl); from 7.60 to 7.90 (mt: the 6H corresponding to the H4 - H8 of the naphthyl and H aromatics of the phtalimido); 7.67 (t, J = 8 Hz, 1H corresponding to the H3 of the naphthyl); 8.06 (d large, J = 9 Hz, 1H each: H7 of the naphthyl); 8.27 (d, J = 8 Hz, 1H: H2 of the naphthyl); 8.86 (s large, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, but using 3.9 g of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-phenylalanine, 1.9 g (70%) of 2(S)-benzyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine are obtained in the form of a yellow solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 383 K, δ in ppm): from 2.85 to 3.60 (mt, 6H: $CONCH_2CH_2NCO$ and $ArCH_2$); from 7.05 to 7.90 (mt, 8H: H3 - H4 - H8 and H aromatics of the phenyl); 8.12 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 8.26 (d, J = 8.5 Hz, 1H: H2 of the naphthyl); 8.91 (d, J = 2 Hz, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 1.9 g of 3 (S)-benzyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, 1 g (58%) of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-benzyl-2-oxo-piperazine is obtained in the form of a beige solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 383 K, δ in ppm): from 2.90 to 3.45 (mt, 6H: $CONCH_2CH_2NCO$ and CH_2Ar); from 6.85 to 7.00 (mt, 2H: H7 and H5 of the naphthyl); from 7.05 to 7.45 (mt, 8H: H2 - H3 - H4 of the naphthyl and H aromatics of the phenyl); 7.52 (d, J = 9 Hz, 1H: H8 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S) -(2-methylthio-ethyl)-2-oxo-piperazine, but using 1 g of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-benzyl-2-oxo-piperazine, 1.8 g (80%) of 3(S)-benzyl-4-[6-(2 (R) -tert-butoxycarbonylaminio-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine are obtained in the form of a yellow solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 393 K, δ in ppm): 1.40 (s, 9H: $OC(CH_3)_3$); from 2.40 to 2.70 (mt: the 2H corresponding to the CH_2S); from 2.90 to 3.65 (mt, 6H: $CONCH_2CH_2NCO$ and CH_2N of the propylamine); 3.16 (d, J = 6 Hz, 2H: CH_2Ar); 3.74 (mt, 1H: CHN of the propylamine); from 4.55 to 5.35 (mf highly spread: 1H corresponding to the NCHCO); 6.75 (s large, 1H: H5 of the naphthyl); from 6.80 to 7.00 (mt, 2H: H4 and H7 of the naphthyl); from 7.10 to 7.45 (mt, 21H: H aromatics of the triphenylmethyl - H aromatics of the phenyl and H3 of the naphthyl); from 7.50 to 7.85 (mt, 2H: H2 and H8 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -3 (S) - (2-methylthio-ethyl) -2-oxo-piperazine, but using 1.8 g of 3(S)-benzyl-4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine, 0.38 g (30%) of trifluoroacetate of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-benzyl-2-oxo-piperazine is obtained in the form of a white power for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): from 2.70 to 3.80 (mt: the 11H corresponding to the $CONCH_2CH_2NCO$ - CH_2Ar - and to the CH_2S and NCH_2CHN of the propylamine); from 4.90 to 5.50 (mf highly spread: 1H corresponding to the NCHCO); from 6.90 to 7.05 (mt, 2H: H7 and H5 of the naphthyl); from 7.15 to 7.40 (mt, 8H: H2 - H3 - H4 of the naphthyl and H aromatics of the phenyl); from 7.60 to 7.75 (mt, 2H: H8 of the naphthyl and CONH).

- ultimate analysis: $C_{25}H_{28}N_4O_2S$, 1.5 CF_3CO_2H

Calculated (%): C = 54.28; H = 4.8; N = 9.04; S = 5.17

Found (%): C = 54.5; H = 4.64; N = 9.21; S = 4.71

EXAMPLE 3: preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-hydroxymethyl-2-oxo-piperazine

By proceeding as in example 1 for the preparation of methyl ester of the N-(2-phtalimido-ethyl)-L-methionine, but using 5 g of the methyl ester chlorhydrate of the O-tert-butyl-L-serine, 5 g (60%) of methyl ester of the O-tert-butyl-N-(2-phtalimido-ethyl)-L-serine are obtained in the form of a white solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.04 (s, 9H: $OC(CH_3)_3$); 2.17 (mt, 1H: NH); 2.68 and 2.84 (2 mts, 1H each: CH_2N); from 3.30 to 3.50 (mt: the 3H corresponding to the CH_2O and NCHCO); from 3.55 to 3.80 (mt, 2H: CH_2-phtalimido); 3.62 (s, 3H: $COOCH_3$); from 7.80 to 7.95 (mt, 4H: H aromatics of the phtalimido).

By proceeding as in example 1 for the preparation of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-methionine, but using 3.83 g of methyl ester of the O-tert-butyl-N-(2-phtalimido-ethyl)-L-serine, 5 g (85%) of methyl ester of the O-tert-butyl-N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-serine are obtained in the form of a white solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 393 K, δ in ppm): from 0.95 to 1.45 (mf, 9H: $OC(CH_3)_3$); from 3.40 to 4.40 (mt, 6H: phtalimidoCH_2CH_2NCO and CH_2O); 3.69 (s: the 3H corresponding to the $COOCH_3$); from 7.55 to 8.25 (mt, 7H: H3 - H4 - H8 of the naphthyl and H aromatics of the phtalimido); 8.05 (d large, J = 9 Hz, 1H: H7 of the naphthyl); 8.30 (d large, J = 8 Hz, 1H: H2 of the naphthyl); 8.91 (s large, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 3 (S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, but using 5 g of methyl ester of the O-tert-butyl-N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-serine, 2.8 g (85%) of 3(S)-tert-butoxymethyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine are obtained in the form of a yellow powder for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 1.22 (s, 9H: $OC(CH_3)_3$); from 3.05 to 4.10 (mt: the H corresponding to the $CONCH_2CH_2NCO$ and OCH_2); from 7.70 to 7.80 (mt, 2H: CONH and H4 of the naphthyl); 7.82 (t, J = 7.5 Hz, 1H: H3 of the naphthyl); 8.12 (d, J = 9 Hz, 1H: H8 of the naphthyl); 8.27 (dd, J = 9 and 2.5 Hz, 1H: H7 of the naphthyl); 8.37 (dd, J = 7.5 and 2 Hz, 1H: H2 of the naphthyl); 9.02 (d, J = 2.5 Hz, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 2.8 g of 3(S)-tert-butoxymethyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, 1.9 g (75%) of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-tert-butoxymethyl-2-oxo-piperazine are obtained in the form of a white solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 393 K, δ in ppm): 1.22 (s, 9H: $OC(CH_3)_3$); from 3.10 to 3.30 - 3.57 and from 3.75 to 4.00 (3 mts: the H corresponding to the $CONCH_2CH_2NCO$ and CH_2O); from 4.55 to 4.90 (mf spread: 1H corresponding to the NCHCO); 5.05 (mf, 2H: NH_2); 6.96 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.00 to 7.10 (mt, 2H: H4 and H7 of the naphthyl); 7.33 (t, J = 8 Hz, 1H: H3 of the naphthyl); 7.53 (mf, 1H: CONH); from 7.50 to 7.65 (mt, 2H: H2 and H8 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 1.7 g of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-tert-butoxymethyl-2-oxo-piperazine, 1.5 g (40%) of 4-[6-(2 (R) -tert-butoxycarbonylamino-3 -triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl]-3(S)-tert-butoxymethyl-2-oxo-piperazine are obtained in the form of a white solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 1.22 (s, 9H: $OC(CH_3)_3$); 1.39 (s, 9H: $COOC(CH_3)_3$); from 2.35 to 2.60 (mt: the 2H corresponding to the CH_2S); from 2.70 to 4.10 (mt: the 9H corresponding to the $CONCH_2CH_2NCO$ - CH_2O and to the NCH_2CHN of the propylamine); from 4.50 to 5.10 (mf highly spread: 1H corresponding to the NCHCO); 5.53 (t,

J = 6 Hz, 1H: NHAr); 6.28 (d large, J = 9 Hz, 1H: NHCOO); 6.79 (d, J = 2 Hz, 1H: H5 of the naphthyl); 6.96 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.07 (d, J = 7.5 Hz, 1H: H4 of the naphthyl); from 7.15 to 7.45 (mt, 16H: H aromatics of the triphenylmethyl and H3 of the naphthyl); 7.60 (mt, 2H: H2 and H8 of the naphthyl); 7.69 (mf, 1H: CONH).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)- 1-naphthyl-carbonyl] -3 (S)- (2-methylthio-ethyl)-2-oxo-piperazine, but using 1.5 g of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 - naphthyl-carbonyl] -3 (S) -tert-butoxymethyl-2-oxo-piperazine, 0.3 g (25%) of trifluoroacetate of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-hydroxymethyl-2-oxo-piperazine are obtained in the form of a white solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): from 2.80 to 3.05 (mt, 2H: CH_2S); from 3.00 to 4.15 (mt: the 9H corresponding to the $CONCH_2CH_2NCO$ - CH_2O - and to the NCH_2CHN of the propylamine); from 4.50 to 5.10 (mf highly spread: 1H corresponding to the NCHCO); 6.98 (d, J = 2 Hz, 1H: H5 of the naphthyl); 7.09 (dd, J = 9 and 2.5 Hz, 1H: H7 of the naphthyl); 7.16 (d, J = 8 Hz, 1H: H4 of the naphthyl); 7.40 (t, J = 8 Hz, 1H: H3 of the naphthyl); from 7.60 to 7.85 (mt, 2H: CONH and H8 of the naphthyl); 7.69 (d, J = 8 Hz, 1H:H2 of the naphthyl).

- ultimate analysis: $C_{19}H_{24}N_4O_3S$, 1.75 CF_3CO_2H

Calculated (%): C = 45.96; H = 4.41; N = 9.53; S = 5.45

Found (%): C = 45.8; H = 5.0; N = 9.74; S = 5.05

EXAMPLE 4: preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-butyl-2-oxo-piperazine

By proceeding as in example 1 for the preparation of methyl ester of the N-(2-phtalimido-ethyl)-L-methionine, but using 5 g of the methyl ester chlorhydrate of the L-norleucine, 5.3 g (60%) of methyl ester of the N-(2-phtalimido-ethyl)-L-norleucine are obtained in the form of a yellow oil for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, δ in ppm): 0.76 (t, J = 6 Hz, 3H: CH_3 of the butyl); 1.17 (mt, 4H: the 2 central CH_2 of the butyl); 1.46 (mt, 2H: CH_2 of the butyl); 2.63 and 2.82 (2 mts, 1H each: CH_2N); 3.24 (t, J = 6 Hz, 1H: NCHCO); from 3.55 to 3.75 (mt, 2H: CH_2-phtalimido); 3.60 (s, 3H: COOCH3); from 7.75 to 7.90 (mt, 4H: H aromatics of the phtalimido).

By proceeding as in example 1 for the preparation of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-methionine, but using 3.8 g of methyl ester of the N-(2-phtalimido-ethyl)-L-norleucine, 5 g (95%) of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-norleucine are obtained in the form of a yellow oil for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 at a temperature of 383 K, δ in ppm): 0.60 to 1.10 (mf, 3H: CH_3 of the butyl); from 1.10 to 2.40 (mf, 6H: the 3 CH_2 of the butyl); from 3.40 to 4.20 (mf, 4H: phtalimidoCH_2CH_2NCO); 3.71 (s, 3H: $COOCH_3$); from 4.20 to 4.80 (mf, 1H: NCHCO); from 7.60 to 8.10 (mt, 7H: H3 - H4 - H8 of the naphthyl and H aromatics of the phtalimido); 8.20 (d large, J = 9 Hz, 1H: H7 of the naphthyl); 8.34 (d, J = 8 Hz, 1H: H2 of the naphthyl); 8.96 (s large, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 3 (S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, but using 5 g of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-norleucine, 2.5 g (75%) of 3(S)-butyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine are obtained in the form of a yellow powder for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 413 K, δ in ppm): 0.91 (t, J = 7 Hz, 3H: CH_3 of the butyl); 1.35 and 1.46 (2 mts, 2H each: the 2 central CH_2 of the butyl); from 1.80 to 2.05 (mt,

2H: CH_2 of the butyl); from 3.15 to 3.45 and from 3.60 to 3.80 (respectively mt and mf spread, 4H completely: $CONCH_2CH_2NCO$); from 4.50 to 4.80 (mf spread, 1H: NCHCO); 7.35 (mf, 1H: CONH); 7.72 (d, J = 8 Hz, 1H: H4 of the naphthyl); 7.78 (t, J = 8 Hz, 1H: H3 of the naphthyl); 8.03 (d, J = 9 Hz, 1H: H8 of the naphthyl); 8.27 (mt, 1H: H7 of the naphthyl); 8.33 (d, J = 8 Hz, 1H: H2 of the naphthyl); 8.96 (s large, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 2.5 g of 3(S)-butyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, 0.8 g (40%) of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-butyl-2-oxo-piperazine is obtained in the form of an ochre solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 0.90 (mf, 3H: CH_3 of the butyl); from 1.20 to 1.55 (mf, 4H: the 2 central CH_2 of the butyl); from 1.75 to 2.05 (mf, 2H: CH_2 of the butyl); from 3.00 to 3.45 (mt, 4H: $CONCH_2CH_2NCO$); from 4.45 to 5.10 (mf highly spread: 1H corresponding to the NCHCO); 5.18 (s large, 2H: NH_2); 6.94 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 6.95 to 7.10 (mt, 2H: H4 and H7 of the naphthyl); 7.33 (t, J = 8 Hz, 1H: H3 of the naphthyl); 7.48 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.54 (mf, 1H: CONH); 7.58 (d, J = 8 Hz, 1H: H2 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S) -(2-methylthio-ethyl)-2-oxo-piperazine, but using 0.8 g of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-butyl-2-oxo-piperazine, 0.9 g (50%) of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-3(S)-butyl-2-oxo-piperazine is obtained in the form of a white solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 383 K, δ in ppm): from 0.80 to 1.00 (mf, 3H: CH_3 of the butyl); from 1.25 to 1.60 (mf, 4H: the 2 central CH_2 of the butyl); 1.40 (s, 9H: $OC(CH_3)_3$); from 1.80 to 2.10 (mf: the 2 H corresponding to the CH_2 of the butyl);

de 2.35 to 2.55 (mt, 2H: CH_2S); from 3.05 to 3.40 (mt, 4H: $CONCH_2CH_2NCO$); 3.15 (d, J = 5.5 Hz, 2H: CH_2N of the propylamine); 3.73 (mt, 1H: CHN of the propylamine); from 4.40 to 5.15 (mf highly spread: 1H corresponding to the NCHCO); 6.80 (d, J = 2 Hz, 1H: H5 of the naphthyl); 6.96 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.05 (d, J = 7.5 Hz, 1H: H4 of the naphthyl); from 7.15 to 7.40 (mt, 16H: H aromatics of the triphenylmethyl and H3 of the naphthyl); 7.48 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.60 (d, J = 8.5 Hz, 1H: H2 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 0.9 g of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-3(S)-butyl-2-oxo-piperazine, 0.33 g (45%) of trifluoroacetate of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-butyl-2-oxo-piperazine is obtained in the form of a white powder for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 383 K, δ in ppm): 0.89 (mf, 3H: CH_3 of the butyl); from 1.15 to 1.60 (mf, 4H: the 2 central CH_2 of the butyl); from 1.75 to 2.10 (mf, 2H: CH_2 of the butyl); from 3.00 to 3.65 (mt, 8H: CH_2N and CH_2S of the propylamine and $CONCH_2CH_2NCO$); from 3.65 to 3.80 (mt, 1H: CHN of the propylamine); from 4.40 to 5.20 (mf highly spread: 1H corresponding to the NCHCO); 6.98 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.05 to 7.15 (mt, 2H: H4 and H7 of the naphthyl); 7.38 (t, J = 8 Hz, 1H: H3 of the naphthyl); 7.56 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.67 (d, J = 8 Hz, 1H: H2 of the naphthyl).

- ultimate analysis: $C_{22}H_{30}N_4O_2S$, 1.33 CF_3CO_2H

Calculated (%): C = 52.31; H = 5.58; N = 9.89; S = 5.66

Found (%): C = 52.48; H = 6.14; N = 9.96; S = 5.4

EXAMPLE 5: preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(R,S)-methoxymethyl-2-oxo-piperazine

A suspension of 5 g of O-methyl-D,L-serine in 50 cm3 of methanol, cooled at a temperature of approximately 4°C, is saturated by hydrochloric acid gas. The reaction mixture is stirred for 1 hour at a temperature of approximately 20°C, then for 1 hour at a temperature of approximately 50°C. The reaction mixture is concentrated under reduced pressure, taken up by 50 cm3 of ethyl ether, spun and dried. 7.2 g (quantitative) of methyl ester chlorhydrate of the O-methyl-D,L-serine are obtained in the form of a white solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 3.30 (s, 3H: OCH_3); from 3.75 to 3.85 (mt, 2H: CH_2O); 3.76 (s, 3H: $COOCH_3$); 4.30 (mt, 1H: NCHCO); 8.76 (mf, 3H: NH_3^+).

By proceeding as in example 1 for the preparation of methyl ester of the N-(2-phtalimido-ethyl)-L-methionine, but using 7.2 g of the methyl ester chlorhydrate of the O-methyl-D,L-serine, 5 g (40%) of methyl ester of the O-methyl-N-(2-phtalimido-ethyl)-D,L-serine are obtained in the form of a colourless oil for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 2.04 (mf, 1H: NH); from 2.75 to 2.90 and 2.94 (2 mts, 1H each: CH_2N); 3.24 (s, 3H: OCH_3); from 3.40 to 3.55 (mt: the 3H corresponding to the CH_2O and NCHCO); 3.64 (s, 3H: $COOCH_3$); from 3.65 to 3.75 (mt, 2H: CH_2-phtalimido); from 7.80 to 7.90 (mt, 4H: H aromatics of the phtalimido).

By proceeding as in example 1 for the preparation of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-methionine, but using 3.06 g of methyl ester of the O-methyl-N-(2-phtalimido-ethyl)-D,L-serine, 3 g (60%) of methyl ester of the O-methyl-N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-D,L-serine are obtained in the form of a yellow oil for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (200 MHz, $(CD_3)_2S0$ d6 at a temperature of 373 K, δ in ppm): from 3.10 to 4.20 (mt: the 6H corresponding to the phtalimidoCH_2CH_2NCO and CH_2O); 3.36 (s large: the 3H corresponding to the OCH_3); 3.72 (s: the 3H corresponding to the $COOCH_3$); from 4.60 to 4.85 (mf spread, 1H:

NCHCO); from 7.60 to 8.10 (mt, 7H: H3 - H4 - H8 of the naphthyl and H aromatics of the phtalimido); 8.19 (mt, 1H: H7 of the naphthyl); 8.33 (d large, J = 8 Hz, 1H: H2 of the naphthyl); 8.94 (d, J = 2 Hz, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 3 (S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, but using 3 g of methyl ester of the O-methyl-N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-D,L-serine, 1.5 g (75%) of 3(R,S)-methoxymethyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine are obtained in the form of an ochre solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 383 K, δ in ppm): from 3.05 to 4.15 (mt, 6H: $CONCH_2CH_2NCO$ and OCH_2); 3.34 (s large, 3H: OCH_3); from 4.55 to 5.10 (mf highly spread, 1H: NCHCO); from 7.65 to 7.85 (mt, 2H: H3 and H4 of the naphthyl); 8.05 (d, J = 9 Hz, 1H: H8 of the naphthyl); 8.27 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 8.32 (mt, 1H: H2 of the naphthyl); 8.97 (d, J = 2 Hz, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 1.5 g of 3(R,S)-methoxymethyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, 1 g (75% *of* 4-(6-amino-1-naphthyl-carbonyl)-3(R,S)-methoxymethyl-2-oxo-piperazine is obtained in the form of a yellow oil for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): from 3.05 to 4.10 (mt, 6H: $CONCH_2CH_2NCO$ and CH_2O); 3.34 (s large, 3H: OCH_3); from 4.50 to 5.00 (mf highly spread: 1H corresponding to the NCHCO); 5.17 (s large, 2H: NH_2); 6.94 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.00 to 7.10 (mt, 2H: H4 and H7 of the naphthyl); 7.33 (t, J = 7.5 Hz, 1H: H3 of the naphthyl); from 7.50 to 7.65 (mt, 2H: H2 and H8 of the naphthyl); 7.73 (mt, 1H: CONH).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S) -(2-methylthio-ethyl)-2-oxo-piperazine,

but using 1 g of 4-(6-amino-1-naphthyl-carbonyl)-3(R,S)-methoxymethyl-2-oxo-piperazine, 1.6 g (70%) of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphénylthio-propylamino)-1-naphthyl-carbonyl]-3(R,S)-methoxymethyl-2-oxo-piperazine are obtained in the form of a yellow solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 1.40 (s, 9H: $OC(CH_3)_3$); 2.36 and from 2.40 to 2.50 (2 mts, 1H each: CH_2S); from 3.00 to 4.05 (mt: the 12H corresponding to the $CONCH_2CH_2NCO$ - CH_2O - OCH_3 and to the NCH_2CHN of the propylamine); from 4.50 to 5.00 (mf highly spread: 1H corresponding to the NCHCO); 5.53 (t, J = 6 Hz, 1H: NHAr); 6.30 (d large, J = 8 Hz, 1H: NHCOO); 6.80 (d, J = 2 Hz, 1H: H5 of the naphthyl); 6.97 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.07 (d, J = 7.5 Hz, 1H: H4 of the naphthyl); from 7.15 to 7.45 (mt, 16H: H aromatics of the triphenylmethyl and H3 of the naphthyl); 7.54 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.60 (d, J = 8 Hz, 1H: H2 of the naphthyl); 7.75 (mt, 1H: CONH).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -3 (S) - (2-méthylthio-ethyl) -2-oxo-piperazine, but using 1.6 g of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1-naphthyl-carbonyl] -3 (R,S) -methoxymethyl-2-oxo- piperazine, 0.23 g (20%) of trifluoroacetate of 4-[6-(2(R)-amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -3 (R,S) -methoxymethyl-2-oxo-piperazine is obtained in the form of a white powder for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 383 K, δ in ppm): from 3.05 to 4.05 (mt, 11H: $CONCH_2CH_2NCO$ - CH_2O and NCH_2CHN and CH_2S of the propylamine); from 4.45 to 4.95 (mf highly spread: 1H corresponding to the NCHCO); 6.96 (d, J = 2 Hz, 1H: H5 of the naphthyl); 7.09 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.13 (d, J = 8 Hz, 1H: H4 of the naphthyl); 7.39 (t, J = 8 Hz, 1H: H3 of the naphthyl); from 7.55 to 7.70 (mt, 2H: H2 and H8 of the naphthyl).

- ultimate analysis: $C_{20}H_{26}N_4O_3S$, 1.4 CF_3CO_2H

Calculated (%): C = 48.72; H = 4.91; N = 9.97; S = 5.70

Found (%): C = 48.40; H = 5.25; N = 9.89; S = 5.40

EXAMPLE 6: preparation of 3(S)-butyl-4-{6-[l-(4-cyanobenzyl)-1H-imidazol-5-yl-methylamino] -1 -naphthyl-carbonyl} -2-oxo-piperazine

To a solution of 5 g of 1H-imidazol-4-yl-carboxaldehyde and 11.17 g of 4-bromomethyl-benzonitrile in 500 cm3 of acetonitrile, 14.37 g of potassium carbonate are added. The reaction mixture is stirred for 2 hours with the acetonitrile reflux, filtered, then concentrated under reduced pressure. The residue is taken up by 100 cm3 of ethyl acetate, washed two times with 30 cm3 of water, then 30 cm3 of a sodium chloride saturated aqueous solution. The solution is dried on magnesium sulphate, filtered, concentrated under reduced pressure. The residue is purified by high-performance liquid chromatography (phase Si 60) by eluting with methylene chloride containing 2.5% methanol. 4.15 g (27%) of l-(4-cyano-benzyl)-1H-imidazol-5-yl-carboxaldehyde and 5.6 g (35%) of 1-(4-cyano-benzyl)-1H-imidazol-4-yl-carboxaldehyde are obtained in the form of yellow solids.

The 1l-(4-cyanobenzyl)-1H-imidazol-5-yl-carboxaldehyde has the following characteristics:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, δ in ppm): 5.62 (s, 2H: CH_2Ar); 7.33 (d, J = 8 Hz, 2H: H2 and H6 of the 4-cyano-phenyl); 7.83 (d, J = 8 Hz, 2H: H3 and H5 of the 4-cyano-phenyl); 7.99 and 8.30 (2 s, 1H each: H aromatics of the imidazolyl); 9.71 (s, 1H: CHO).

The l-(4-cyanobenzyl)-1H-imidazol-4-yl-carboxaldehyde has the following characteristics:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, δ in ppm): 5.43 (s, 2H: CH_2Ar); 7.50 (d, J = 8 Hz, 2H: H2 and H6 of the 4-cyano-phenyl); 7.88 (d, J = 8 Hz, 2H: H3 and H5 of the 4-cyano-phenyl); 8.03 and 8.16 (2 s, 1H each: H aromatics of the imidazolyl); 9.73 (s, 1H: CHO).

To a solution composed of 0.49 g of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-butyl-2-oxo-piperazine in 45 cm3 of acetonitrile and 0.4 cm3 of acetic acid, 0.348 g of 1-(4-cyanobenzyl)-1H-imidazol-5-yl-carboxaldehyde and molecular sieve (4Å) are added. The reaction mixture is stirred for 3 hours at a temperature of approximately 20°C, then 0.145 g of sodium cyanoborohydride is added. The reaction mixture is stirred for 96 hours at a temperature of approximately 20°C, filtered, then concentrated under reduced pressure. The residue is purified by high-performance liquid chromatography (phase Cl8) by eluting with an acetonitrile-water mixture containing 0.07% of trifluoroacetic acid. 0.18 g (15%) of ditrifluoroacetate of 3(S)-butyl-4-{6-[1-(4-cyanobenzyl)-1H-imidazol-5-yl-methylamino]-1-naphthyl-carbonyl}-2-oxo-piperazine is obtained in the form of a beige powder for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 383 K, δ in ppm): 0.89 (mt, 3H: CH_3 of the butyl); from 1.20 to 1.55 (mt, 4H: the 2 central CH_2 of the butyl); from 1.75 to 2.05 (mt: the 2 H corresponding to the CH_2 of the butyl); from 3.10 to 3.40 (mt, 4H: $CONCH_2CH_2NCO$); from 4.30 to 4.90 (mf highly spread: 1H corresponding to the NCHCO); 4.41 (s, 2H: CH_2Nnaphthyl); 5.61 (s, 2H: NCH_2Ar); 7.02 (d, J = 9 Hz, 1H: H7 of the naphthyl); 7.10 (d, J = 7.5 Hz, 1H: H4 of the naphthyl); 7.38 (t, J = 7.5 Hz, 1H: H3 of the naphthyl); 7.46 (d, J = 8 Hz, 2H: H2 and H6 of the 4-cyano-phenyl); 7.52 (s large, 1H: N-CH=C of the imidazolyl); 7.54 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.63 (d, J = 7.5 Hz, 1H: H2 of the naphthyl); 7.78 (d, J = 8 Hz, 2H: H3 and H5 of the 4-cyano-phnyl); 8.77 (s large, 1H: N=CH-N of the imidazolyl).

- ultimate analysis: $C_{31}H_{32}N_6O_2$, 2.25 CF_3CO_2H

Calculated (%): C = 54.86; H = 4.44; N = 10.81

Found (%): C = 54.55; H = 4.95; N = 10.8

EXAMPLE 7: preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-methyl-2-oxo-piperazine

By proceeding as in example 1 for the preparation of methyl ester of the N-(2-phtalimido-ethyl)-L-methionine but using the methyl ester of L-alanine (10 g, 0.071 mole), 10.2 g (52%) of methyl ester of N-(2-phtalimido-ethyl)-L-alanine are obtained in the form of a white powder.

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.14 (d, J = 7 Hz, 3H: CH_3); 2.25 (mf, 1H: NH); from 2.55 to 2.90 (mt, 2H: CH_2N); from 3.30 to 3.45 (mt: 1H corresponding to the NCHCO); from 3.55 to 3.75 (mt, 2H: CH_2-phtalimido); 3.60 (s, 3H: $COOCH_3$); from 7.80 to 8.00 (mt, 4H: H aromatics of the phtalimido).

By proceeding as in example 1 for the preparation of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-methionine, but using 4.4 g (0.0159 mole) of methyl ester of the N-(2-phtalimido-ethyl)-L-alanine, 3.5 g (51%) of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-alanine are obtained in the form of a pink meringue for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 at a temperature of 383 K, δ in ppm): from 1.40 to 1.90 (mf, 3H: CH_3); from 3.40 to 4.10 (mt, 4H: phtalimidoCH_2CH_2NCO); 3.70 (s, 3H: $COOCH_3$); from 4.40 to 4.70 (mf, 1H: CONCHCO); from 7.60 to 8.20 (mt, 7H: H3 - H4 - H8 of the naphthyl and H aromatics of the phtalimido); 8.17 (d large, J = 9 Hz, 1H: H7 of the naphthyl); 8.32 (d, J = 8.5 Hz, 1H: H2 of the naphthyl); 8.92 (s large, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, but using 3.5 g (0.0073 mole) of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-alanine, 1.9 g (83%) of 3(S)-methyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine are obtained in the form of an orangey solid for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 423 K, δ in ppm): 1.51 (d, J = 7 Hz, 3H: CH_3); from 3.15 to 3.50 and from 3.65 to 3.85 (respectively mt and mf, 3H and 1H: $CONCH_2CH_2NCO$); 4.61 (mf, 1H: NCHCO); 7.86 (mf, 1H: CONH); from 7.70 to 7.90 (mt, 2H: H3 and H4 of the naphthyl); 8.03 (d, J = 9 Hz, 1H: H8 of the naphthyl); from 8.20 to 8.35 (mt, 2H: H2 and H7 of the naphthyl); 8.94 (s large, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 0.9 g (0.0028 mole) of 3(S)-methyl-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, 0.9 g (100%) of 4-(6-amino-1-naphthyl-carbonyl)-3 (S)-methyl-2-oxo-piperazine is obtained in the form of a pinkish meringue for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 383 K, δ in ppm): 1.44 (mt, 3H: CH_3); from 3.00 to 3.90 (mt: the 4H corresponding to the $CONCH_2CH_2NCO$); from 4.25 to 5.00 (mf spread, 1H: NCHCO); from 6.95 to 7.10 (mt, 2H: H4 and H7 of the naphthyl); 7.35 (dd, J = 8 and 7.5 Hz, 1H: H3 of the naphthyl); 7.50 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.60 (d, J = 8 Hz, 1H: H2 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S) -(2-methylthio-ethyl)-2-oxo-piperazine, but using 0.9 g (0.0032 mole) of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-methyl-2-oxo-piperazine, 0.89 g (39%) of 4- [6- (2 (R) -tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl]-3 (S)-methyl-2-oxo-piperazine is obtained for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 1.40 (s, 9H: $OC(CH_3)_3$); 1.45 (mt, 3H: CH_3); from 2.35 to 2.55 (mt, 2H: CH_2S); from 3.05 to 3.40 (mt, 4H: $CONCH_2CH_2NCO$); 3.16 (mt, 2H: CH_2N of the propylamine); 3.74 (mt, 1H: CHN of the propylamine); from 4.40 to 4.90 (mf highly spread: 1H corresponding to the NCHCO); 5.57 (t, J = 6 Hz, 1H: NHAr); 6.32 (d large, J = 8.5 Hz, 1H: NHCOO); 6.80 (d, J = 2 Hz, 1H: H5 of the naphthyl); 6.97 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.06 (d large, J = 7.5 Hz, 1H: H4 of the naphthyl); from 7.15 to 7.40 (mt, 16H: H aromatics of the triphenylmethyl and H3 of the naphthyl); 7.47 (d, J = 9 Hz, 1H: H8 of the naphthyl); from 7.55 to 7.70 (mt, 1H: CONH); 7.60 (d, J = 8 Hz, 1H: H2 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 0.89 g (0.0012 mole) of trifluoroacetate of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-3(S)-methyl-2-oxo-piperazine, 0.093 g (12%) of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-methyl-2-oxo-piperazine is obtained in the form of a white freeze-dried product for which the characteristics are as follows:

- DCI mass spectrum (NH_3): M/Z = 373 $(M+H)^+$

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 1.44 (d large, J = 6.5 Hz, 3H: CH_3); from 2.90 to 3.65 (mt: the 9H corresponding to the $CONCH_2CH_2NCO$ and to the NCH_2CHN and CH_2S of the propylamine); from 4.20 to 4.85 (mf highly spread, 1H: NCHCO); 6.98 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.05 to 7.15 (mt, 2H: H4 and H7 of the naphthyl); 7.41 (dd, J = 8 and 7.5 Hz, 1H: H3 of the naphthyl); 7.55 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.62 (mf, 1H: CONH); 7.70 (d, J = 8 Hz, 1H: H2 of the naphthyl).

- ultimate analysis: $C_{19}H_{24}N_4O_2S$, 1.6 CF_3CO_2H

Calculated (%): C = 48.00; H = 4.65; N = 10.10; S = 5.78

Found (%): C = 48.04; H = 4.72; N = 10.24; S = 5.35

EXAMPLE 8: preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine

By proceeding as in example 1 for the preparation of methyl ester of the N-(2-phtalimido-ethyl)-L-methionine, but using 7.0 g (0.056 mole) of methyl ester chlorhydrate of glycine, 7.2 g (49%) of methyl ester of N-(2-phtalimido-ethyl) -glycine are obtained in the form of a white powder.

-magnetic nuclear resonance spectrum of the proton (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 2.21 (s large, 1H: NH); 2.78 (t, J = 6.5 Hz, 2H: CH_2N); 3.34 (s, 2H: NCH_2CO); 3.60 (s, 3H: $COOCH_3$); 3.66 (t, J = 6.5 Hz, 2H: CH_2-phtalimido); from 7.80 to 7.90 (mt, 4H: H aromatics of the phtalimido).

By proceeding as in example 1 for the preparation of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-methionine, but using 4 g (0.0138 mole) of methyl ester of N-(2-phtalimido-ethyl)-glycine, 9 g (100%) of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2- phtalimido-ethyl) -glycine are obtained for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (300 MHz, $(CD_3)_2SO$ d6, δ in ppm). The description is carried out on a mixture of two rotamers 80-20.

de 3.20 to 4.05 (mt, 4H completely: phtalimidoCH_2CH_2NCO); 3.46 - 3.80 and 4.47 (3 s, 5H completely: $CONCH_2COOCH_3$); from 7.35 to 8.40 (mt, 4H completely: H2 - H3 - H4 and H8 of the naphthyl); 7.61 - 7.78 - 7.88 and 7.98 (4 mts, 4H completely: H aromatics of the phtalimido); 8.11 and 8.33 (respectively dd, J = 9.5 and 2.5 Hz and d large, J = 8.5 Hz, 1H completely: H7 of the naphthyl); 8.98 and 9.04 (respectively s large and d, J = 2.5 Hz, 1H completely: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, but using 9 g (0.0195 mole) of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-glycine, 2.5 g (43%) of 4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine are obtained in the form of a beige powder for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CF_3COOD d1, at a temperature of 383 K, δ in ppm): from 3.15 to 3.40 and from 3.40 to 3.80 (2 mf, 2H each: $CONCH_2CH_2NCO$); from 3.85 to 4.30 (mf, 2H: $CONCH_2CO$); from 7.65 to 7.85 (mt, 2H: H3 and H4 of the naphthyl); 8.05 (d, J = 9 Hz, 1H: H8 of the naphthyl); 8.26 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 8.34 (mt, 1H: H2 of the naphthyl); 8.98 (d, J = 2 Hz, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-(6-amino-1- naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 2.5 g (0.0083 mole) of 4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, 3 g of 4-(6-amino-1-naphthyl-carbonyl)-2-oxo-piperazine are obtained in the form of a brown meringue used without any additional purification in the later steps.

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 3.25 and from 3.45 to 3.75 (respectively mf and mf spread: the 4H corresponding to the $CONCH_2CH_2NCO$); from 3.90 to 4.20 (mf spread, 2H: $CONCH_2CON$); from 4.80 to 5.70 (mf highly spread: 2H corresponding to the NH_2); 6.96 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.00 to 7.10 (mt, 2H: H4 and H7 of the naphthyl); 7.34 (t, J = 8 Hz, 1H: H3 of the naphthyl); 7.52 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.60 (d, J = 8 Hz, 1H: H2 of the naphthyl); 7.72 (mf, 1H: CONH).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-3(S)- (2-methylthio-ethyl)-2-oxo-piperazine, but using 1 g (0.0037 mole) of 4-(6-amino-1-naphthyl-carbonyl)-2-oxo-piperazine, 1.36 g (52%) of 4-[6-(2(R)-tert-butoxycarbonylamino- 3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -2-oxo-piperazine are obtained for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 1.40 (s, 9H: $OC(CH_3)_3$); 2.45 and 2.52 (respectively dd, J = 12 and 6 Hz and mt, 1H each: CH_2S); from 3.10 to 3.30 (mt, 4H: $CONCH_2CH_2NCO$); from 3.40 to 3.70 (mf, 2H: CH_2N of the propylamine); 3.76 (mt, 1H: CHN of the propylamine); from 3.90 to 4.15 (mf, 2H: $CONCH_2CON$); 5.46 (t, J = 6 Hz, 1H: NHAr); 6.21 (d large, J = 8 Hz, 1H: NHCOO); 6.81 (d, J = 2 Hz, 1H: H5 of the naphthyl); 6.97 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.07 (d, J = 8 Hz, 1H: H4 of the naphthyl); from 7.15 to 7.40 (mt, 16H: H aromatics of the triphenylmethyl and H3 of the naphthyl); 7.50 (d, J = 9 Hz, 1H: H8 of the naphthyl); from 7.55 to 7.65 (mt, 1H: CONH); 7.60 (d, J = 8 Hz, 1H: H2 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)- amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 0.81 g (0.0011 mole) of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine, 0.067 g (12%) of trifluoroacetate of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine is obtained in the form of a white freeze-dried product for which the characteristics are as follows:

- DCI mass spectrum (NH_3): M/Z = 359 $(M+H)^+$

- magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): from 2.70 to 3.80 (mt: the 9H corresponding to the $CONCH_2CH_2NCO$ – to the NCH_2CHN and CH_2S of the propylamine); from 3.85 to 4.15 (mf spread, 2H: $CONCH_2CON$); 6.98 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.05 to 7.20 (mt, 2H: H4 and H7 of the naphthyl); 7.41 (dd, J = 8 and 7.5 Hz, 1H: H3 of the naphthyl); 7.58 (d, J = 9 Hz, 1H: H8 of the naphthyl); from 7.65 to 7.80 (mt, 1H: CONH); 7.70 (d, J = 8 Hz, 1H: H2 of the naphthyl).

- ultimate analysis: $C_{18}H_{22}N_4O_2S$, 1.3 CF_3CO_2H

Calculated (%): C = 48.83; H = 4.63; N = 11.06; S = 6.32

Found (%): C = 48.64; H = 4.84; N = 11.26; S = 5.95

EXAMPLE 9: preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl-1-methyl-3(S)-methylthioethyl-2-oxo-piperazine

To 0.12 g (0.0042 mole) of sodium hydride in suspension in 15 ml of anhydrous tetrahydrofuran under argon, 1.3 g (0.0035 mole) of 3 (S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine is added and stirring is continued at a temperature of approximately 20°C for 1 hour. 0.26 ml (0.0042 mole) of methyl iodide is then added to the reaction medium and the reaction is continued for one night at the same temperature. After dry concentration, the residue is purified by flash chromatography on silica column by eluting with an acetonitrile-water mixture containing 0.07% of trifluoroacetic acid.

0.7 g (0.0018 mole) of 1-methyl-3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine in a solution in 75 ml of dimethylformamide in an autoclave are heated at 60°C for 5 hours in a hydrogen atmosphere in the presence of 50 mg of 5% palladium on carbon. After cooling, the reaction medium is filtered over celite and the filtrate is dry concentrated. The crude product (2.5 g) is purified par chromatography on silica column by eluting with ethyl acetate. In this way, 0.25 g (31%) of 1-methyl-3(S)-(2-methylthio-ethyl)-4-(6-amino-1-naphthyl-carbonyl)-2-oxo-piperazine is obtained for which the characteristics are as follows:

49

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6 with the addition of a few drops of CD_3COOD d4, at a temperature of 383 K, δ in ppm): from 1.95 to 2.35 (mf, 2H: CH_2 of the methyl-thio-ethyl); 2.06 (s large, 3H: SCH_3); from 2.50 to 2.70 (mt, 2H: CH_2S); 2.91 (s, 3H: NCH_3); from 3.05 to 3.55 (mt: the H corresponding to the $CONCH_2CH_2NCO$); 6.97 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.00 to 7.10 (mt, 2H: H4 and H7 of the naphthyl); 7.33 (t, J = 7.5 Hz, 1H: H3 of the naphthyl); 7.47 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.59 (d, J = 7.5 Hz, 1H: H2 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S) -(2-methylthio-ethyl)-2-oxo-piperazine, but using 0.25 g (0.7 mmole) of 1-methyl-3(S)-(2-methylthio-ethyl)-4-(6-amino-1-naphthyl-carbonyl)-2-oxo-piperazine, 0.164 g (29%) of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-1-methyl-3(S)-methylthioethyl- 2-oxo-piperazine is obtained for which the characteristics are as follows:

- DCI mass spectrum (NH_3): M/Z = 789 $(M+H)^+$; M/Z = 806 $(M+NH_4)^+$

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2- oxo-piperazine, but using 0.164 g (0.2 mmole) of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethlthio-propylamino)-1-naphthyl-carbonyl]-1-methyl-3(S)-methylthioethyl-2-oxo-piperazine, 0.025 g (22%) of trifluoroacetate of 4- [6- (2 (R) -amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -1 -methyl-3 (S)-methylthioethyl-2-oxo-piperazine is obtained in the form of a white freeze-dried product for which the characteristics are as follows:

- DCI mass spectrum (NH_3): M/Z = 447 $(M+H^+)$

- magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): from 1.95 to 2.35 (mf, 2H: CH_2 of the methyl-thio-ethyl); 2.07 (mf, 3H: SCH_3); from 2.50 to 2.75 (mf, 2H: CH_2S of the methyl-thio-ethyl); from 2.75 to 3.80 (mt: the 9H corresponding to the $CONCH_2CH_2NCO$ and to the

NCH_2CHN and CH_2S of the propylamine); 2.91 (s: the 3H corresponding to the NCH_3); from 4.60 to 5.10 (mf highly spread: 1H corresponding to the NCHCO); from 6.95 to 7.00 (mt, 1H: H5 of the naphthyl); from 7.05 to 7.20 (mt, 2H: H4 and H7 of the naphthyl); 7.40 (mt, 1H: H3 of the naphthyl); 7.55 (d large, J = 9 Hz, 1H: H8 of the naphthyl); from 7.65 to 7.75 (mt, 1H: H2 of the naphthyl).

- ultimate analysis: $C_{22}H_{30}N_4O_2S_2,1.5\ CF_3CO_2H$

Calculated (%): C = 48.61; H = 5.14; N = 9.07; S = 10.38

Found (%): C = 48.80; H = 4.85; N = 9.40; S = 10.31

EXAMPLE 10: preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-1-benzyl-3(S)-methylthioethyl-2-oxo-piperazine

By proceeding as in example 9 for the preparation of 1-methyl-3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, but using 0.5 g (1.33 mmoles) of 3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine and 0.19 ml (1.6 mmoles) of benzyl bromide, 0.23 g (37%) of 1-benzyl-3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine is obtained in the form of a rust meringue for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): from 2.00 to 2.45 (mf, 2H: CH_2 of the methyl-thio-ethyl); 2.09 (mf: the 3H corresponding to the SCH_3); from 2.55 to 2.85 (mf, 2H: SCH_2); from 3.10 to 3.65 (mt: the H corresponding to the $CONCH_2CH_2NCO$); 4.60 (AB, J = 15 Hz, 2H: $ArCH_2$); from 7.25 to 7.45 (mt, 5H: H aromatics of the phenyl); from 7.75 to 7.85 (mt, 2H: H3 and H4 of the naphthyl); 7.96 (d, J = 9 Hz, 1H: H8 of the naphthyl); 8.23 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 8.37 (mt, 1H: H2 of the naphthyl); 9.01 (d, J = 2 Hz, 1H: H5 of the naphthyl).

By proceeding as in example 9 for the preparation of 1-methyl-3(S)-(2-methylthio-ethyl)-4-(6-amino-1-naphthyl-carbonyl)-2-oxo-piperazine, but using 0.78 g (1.68 mmoles) of 1-benzyl-3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, 0.3 g (41%) of 1-benzyl-3(S)-(2-methylthio-

ethyl) -4- (6-amino-1 -naphthyl-carbonyl) -2-oxo-piperazine is obtained in the form of an orangey meringue for which the characteristics are as follows:

- DCI mass spectrum (NH_3): M/Z = 434 $(M+H)^+$

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S) -(2-methylthio-ethyl)-2-oxo-piperazine, but using 0.3 g (0.69 mmole) of 1 -benzyl-3 (S) - (2-methylthio-ethyl)-4- (6-amino-1-naphthyl-carbonyl) -2-oxo-piperazine, 0.093 g (15%) of 1-benzyl-4-[6-(2(R)-tert-butoxycarbonyl-amino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S) -methylthio-ethyl-2-oxo- piperazine is obtained for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): 1.41 (s, 9H: $OC(CH_3)_3$); 2.09 (mf, 3H: SCH_3); from 2.10 to 2.75 (mt, 6H: the 2 CH_2S and CH_2 of the methyl-thio-ethyl); from 2.90 to 3.55 (mt, 6H: $CONCH_2CH_2NCO$ and CH_2N of the propylamine); 3.74 (mt, 1H: CHN of the propylamine); from 4.40 to 5.20 (mf highly spread: 1H corresponding to the NCHCO); 4.58 (s large, 2H: $ArCH_2$); 5.56 (t, J = 6 Hz, 1H: NHAr); 6.32 (d large, J = 8.5 Hz, 1H: NHCOO); 6.79 (d, J = 2 Hz, 1H: H5 of the naphthyl); 6.91 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.06 (d, J = 7.5 Hz, 1H: H4 of the naphthyl); from 7.15 to 7.50 (mt, 22H: H aromatics of the triphenylmethyl - H aromatics of the phenyl - H3 and H8 of the naphthyl); 7.60 (d, J = 8.5 Hz, 1H: H2 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 0.093 g (0.11 mmole) of 1-benzyl-4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S) - methylthioethyl-2-oxo-piperazine, 0.037 g (54%) of trifluoroacetate of 4- [6- (2 (R) -amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-1-benzyl-3 (S) -methylthioethyl-2-oxo-piperazine is obtained in the form of a white freeze-dried product for which the characteristics are as follows:

- DCI mass spectrum (NH_3): M/Z = 523 $(M+H)^+$

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): from 2.00 to 2.35 (mt, 2H: CH_2 of the methyl-thio-ethyl); 2.08 (mf, 3H: SCH_3); from 2.50 to 2.75 (mf, 2H: CH_2S of the methyl-thio-ethyl); from 2.75 to 3.65 (mt: the 8H corresponding to the $CONCH_2CH_2NCO$ and to the CH_2N and CH_2S of the propylamine); 3.68 (mt, 1H: CHN of the propylamine); 4.58 (s, 2H: $ArCH_2$); from 4.60 to 5.20 (mf highly spread: 1H corresponding to the NCHCO); 6.96 (d, J = 2 Hz, 1H: H5 of the naphthyl); 7.05 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.12 (d, J = 7.5 Hz, 1H: H4 of the naphthyl); from 7.20 to 7.45 (mt, 6H: H aromatics of the phenyl and H3 of the naphthyl); 7.49 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.67 (d, J = 8.5 Hz, 1H: H2 of the naphthyl).

- ultimate analysis: $C_{28}H_{34}N_4O_2S_2,1.6\ CF_3CO_2H$

Calculated (%): C = 53.14; H = 5.09; N = 7.95; S = 9.09

Found (%): C = 53.37; H = 4.75; N = 7.98; S = 8.72

EXAMPLE 11: preparation of 4-[6-(1-methyl-1H-imidazol-5-yl-methylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine

By proceeding as in example 6 for the preparation of 1-(4-cyano-benzyl)-1H-imidazol-5-yl-carboxaldehyde and 1-(4-cyano-benzyl)-1H-imidazol-4-yl-carboxaldehyde, but using 3.6 g (0.037 mole) of 1H-imidazol-4-yl-carboxaldehyde and 2.56 ml (0.041 mole) of methyl iodide, 0.81 g (19%) of 1-methyl-1H-imidazol-5-yl-carboxaldehyde is obtained in the form of a white solid for which the characteristics are as follows:

N.M.R. spectrum ^1H (300 MHz, $(CD_3)_2SO$ d6, d in ppm): 3.87 (s, 3H: NCH_3); 7.88 (s, 1H: N=CH-N); 8.01 (s, 1H: N-CH=); 9.75 (s, 1H: CHO).

By proceeding as in example 6 for the preparation of 3(S)-butyl-4-{6-[1-(4-cyanobenzyl)-1H-imidazol-5-yl-methylamino]-1-naphthyl-carbonyl}-2-oxo-piperazine, but using 0.2 g (0.58 mmole) of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine and 0.077 g (0.7 mmole) of 1-methyl-1H-imidazol-5-yl-carboxaldehyde, 0.027 g (8%) of trifluoroacetate of 4-[6-(1-methyl-1H-imidazol-5-yl-methylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-methyl)-2-oxo-piperazine is obtained in the form of a white powder for which the characteristics are as follows:

- DCI mass spectrum (NH_3): M/Z = 438 $(M+H)^+$

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 373 K, δ in ppm): from 1.95 to 2.35 (mt: the 5H corresponding to the CH_2 of the methyl-thio-ethyl and to the SCH_3); from 2.55 to 2.80 (mf, 2H: CH_2S); from 2.80 to 3.75 (mf: the 4H corresponding to the $CONCH_2CH_2NCO$); 3.91 (s, 3H: NCH_3); 4.54 (s, 2H: CH_2Nnaphthyl); from 4.65 to 5.15 (mf highly spread: 1H corresponding to the NCHCO); 7.02 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.10 to 7.20 mt, 2H: H4 and H7 of the naphthyl); 7.40 (t, J = 8 Hz, 1H: H3 of the naphthyl); from 7.50 to 7.60 (mt, 1H: CONH); 7.54 (d, J = 9 Hz, 1H: H8 of the naphthyl); from 7.65 to 7.75 (mt, 1H: N-CH=C of the imidazolyl); 7.70 (d, J = 8 Hz, 1H: H2 of the naphthyl); 8.86 (s large, 1H: N=CH-N of the imidazolyl).

- ultimate analysis: $C_{23}H_{27}N_5O_2S$, 1.6 CF_3CO_2H

Calculated (%): C = 50.76; H = 4.65; N = 11.30; S = 5.17

Found (%): C =50.90; H = 4.83; N = 11.23; S = 5.04

EXAMPLE 12: preparation of 3(S)-(2-carbamoyl-ethyl)-4-[6-(2(R)-amino-3-mercapto-propylamino)-1 -naphthyl-carbonyl] -2-oxo-piperazine

By proceeding as in example 1 for the preparation of methyl ester of the N-(2-phtalimido-ethyl)-L-methionine, but using 3.28 g (12.9 mmoles) of methyl ester chlorhydrate of L-[N-ω-di(4-methoxyphenyl)methyl]-asparagine, 1.89 g (26%) of methyl ester of L-N-α-(2-phtalimido-ethyl)-[N-ω-di(4-methoxyphenyl)methyl]-asparagine are obtained in the form of a white powder.

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 353 K, δ in ppm): 1.78 (mt, 2H: CH_2); 2.10 (mf, 1H: NH); 2.26 (t, J = 7.5 Hz, 2H: CH_2CO); 2.68 and 2.83 (2 mts, 1H each: CH_2N); 3.27 (t large, J = 6 Hz, 1H: NCHCO); from 3.55 to 3.70 (mt, 2H: CH_2-phtalimido); 3.61 s, 3H: $COOCH_3$); 3.75 and 3.76 (2 s, 3H each: the 2 $ArOCH_3$); 6.02 (d, J = 9 Hz, 1H: CHN of the bis-[4-methoxyphenyl]-methyl); from 6.80 to 6.95 and from 7.10 to 7.20 (respectively mt and d, J = 9 Hz, 4H each: H aromatics of the bis-[4-methoxyphenyl]-methyl); from 7.80 to 7.95 (mt, 4H: H aromatics of the phtalimido); 8.35 (d large, J = 9 Hz, 1H: CONH).

By proceeding as in example 1 for the preparation of methyl ester of the N-(6-nitro-1-naphthyl-carbonyl)-N-(2-phtalimido-ethyl)-L-methionine, but using 3.77 g (6.7 mmoles) of methyl ester of L-N-α-(2-phtalimido-ethyl)-[N-ω-di(4-methoxyphenyl)methyl]-asparagine, 3 g (59%) of methyl ester of the L-N-α- (6-nitro-1 -naphthyl-carbonyl) -N-α- (2-phtalimido-ethyl) -[N-ω-di(4-methoxyphenyl)methyl]-asparagine are obtained.

By proceeding as in example 1 for the preparation of 3(S)-(2-methylthio-ethyl)-4-(6-nitro-1-naphthyl-carbonyl)-2-oxo-piperazine, but using 3 g (3.95 mmoles) of methyl ester of the L-N-α-(6-nitro-1-naphthyl-carbonyl)-N-α-(2- phtalimido-ethyl)-[N-ω-di(4-methoxyphenyl)methyl]-asparagine, 2 g (85%) of 3 (S) - {2- [N-di (4-methoxyphenyl) methyl] carbamoyl} ethyl-4- (6-nitro-1 -naphthyl- carbonyl)-2-oxo-piperazine are obtained in the form of a yellow powder for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): from 2.05 to 2.60 (mt, 4H: CH_2CH_2CON); from 2.75 to 3.65 (mt: the 4H corresponding to the $CONCH_2CH_2NCO$); 3.76 (s, 6H: the 2 $ArOCH_3$); 6.06 (d large, J = 7.5 Hz, 1H: CHN of the bis-[4-methoxyphenyl]-methyl); 6.88 and 7.19 (2d, 4H each: H aromatics of the bis-[4-methoxyphenyl]-methyl); 7.66 (mf, 1H: CONH); from 7.70 to 7.80 (mt, 2H: H3 and H4 of the naphthyl); 8.04 (d, J = 9 Hz, 1H: H8 of the naphthyl); from 8.20 to 8.35 (mt, 1H: CONH); 8.25 (dd, J = 9 and 2.5 Hz, 1H: H7 of the naphthyl); 8.35 (mt, 1H: H2 of the naphthyl); 9.00 (d, J = 2.5 Hz, 1H: H5 of the naphthyl).

By proceeding as in example 1 for the preparation of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 1.8 g (3 mmoles) of 3 (S) - {2-[N-di (4-methoxyphenyl) methyl] carbamoyl} ethyl-4- (6-nitro-1 -naphthyl-carbonyl)-2-oxo-piperazine, 2 g of 3 (S)-{2-[N-di (4-methoxyphenyl)methyl]carbamoyl}ethyl-4-(6-amino-1-naphthyl-carbonyl)-2-oxo-piperazine are obtained in the form of a brown powder used without any additional purification in the later steps.

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 423 K, δ in ppm): from 2.10 to 2.35 (mt, 2H: CH_2); 2.44 (mt, 2H: CH_2CO); 3.15 - 3.25 - 3.36 and 3.66 (4 mts, 1H each: $CONCH_2CH_2NCO$); 3.78 (s, 6H: the 2 $ArOCH_3$); 4.72 (mf, 1H: NCHCO); from 4.70 to 5.10 (mf spread, 2H: NH_2); 6.06 (d, J = 8.5 Hz, 1H: CHN of the bis-[4-methoxyphenyl]-methyl); 6.87 and 7.20 (2 d, J = 8 Hz, 4H each: H aromatics of the bis-[4-methoxyphenyl]-methyl); 6.98 (d, J = 2 Hz, 1H: H5 of the naphthyl); from 7.00 to 7.10 (mt, 2H: H4 and H7 of the naphthyl); 7.25 (mf, 1H: CONH); 7.30 (t, J = 8 Hz, 1H: H3 of the naphthyl); 7.52 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.58 (d, J = 8 Hz, 1H: H2 of the naphthyl); from 7.80 to 7.95 (mt, 1H: the other CONH).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino) -1 -naphthyl-carbonyl] -3 (S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 1.7 g (3 mmoles) of 3(S)-{2-[N-di(4-methoxyphenyl)methyl]carbamoyl}ethyl-4-(6-amino-1-naphthyl-carbonyl)-2-oxo-piperazine, 1.2 g (40%) of 3(S)-{2-[N-di(4-methoxyphenyl) methyl]carbamoyl} ethyl-4- [6-(2 (R) -tert-butoxycarbonylamino-3-triphenylmethyl-thio-propylamino)-1-naphthyl-carbonyl] -2-oxo-piperazine are obtained in the form of a white powder for which the characteristics are as follows:

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 403 K, δ in ppm): 1.40 (s, 9H: $OC(CH_3)_3$); from 2.10 to 2.35 (mt, 2H: CH_2); from 2.35 to 2.60 (mt: the 4H corresponding to the CH_2S and CH_2CO); from 3.05 to 3.30 - 3.36 and from 3.50 to 3.70 (respectively 2 mts and mf spread, 4H completely: $CONCH_2CH_2NCO$); 3.19 (t, J = 5.5 Hz, 2H: CH_2N of the propylamine); from 3.70 to 3.80 (mt, 1H: CHN of the propylamine); 3.76 (s, 6H: the 2 $ArOCH_3$); from 4.55 to 4.95 (mf spread, 1H: NCHCO); 5.31 (t, J = 5.5 Hz, 1H: NHAr); from 6.00 to 6.10 (mt, 2H: NHCOO and CHN of the bis-[4-methoxyphenyl]-methyl); 6.81 (d, J = 2 Hz, 1H: H5 of the naphthyl); 6.88 (d, J = 9 Hz, 4H: H3 and H5 of the bis-[4-methoxyphenyl]-methyl); 6.94 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.06 (d, J = 7.5 Hz, 1H: H4 of the naphthyl); from 7.15 to 7.45 (mt, 21H: H aromatics of the triphenylmethyl - H2 and H6 of the bis-[4-methoxyphenyl]-methyl - H3 of the naphthyl and CONH); 7.50 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.59 (d, J = 8 Hz, 1H: H2 of the naphthyl); 8.04 (d large, J = 7.5 Hz, 1H: CONH).

By proceeding as in example 1 for the preparation of 4-[6-(2(R)- amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine, but using 1.2 g (1.2 mmoles) of 3(S)-{2-[N-di(4-methoxyphenyl)methyl]carbamoyl}ethyl-4-[6-(2(R)-tert-butoxycarbonylamino-3-triphenylmethylthio-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine, 0.196 g (30%) of trifluoroacetate of 3(S)-(2-carbamoyl-ethyl)-4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine are obtained in the form of a white freeze-dried product for which the characteristics are as follows:

- DCI mass spectrum (NH_3): M/Z = 430 $(M+H)^+$

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 363 K, δ in ppm): from 2.00 to 2.50 (mt, 4H: CH_2CH_2CO); 2.88 and 2.96 (2 dd, J = 15 and 5.5 Hz, 1H each: CH_2S); from 2.95 to 3.70 (mt: the 7H corresponding to the $CONCH_2CH_2NCO$ and to the NCH_2CHN of the propylamine); from 4.75 to 5.15 (mf highly spread: 1H corresponding to the NCHCO); from 6.50 to 6.90 (mf highly spread: the 2H corresponding to the $CONH_2$); 6.98 (d, J = 2 Hz, 1H: H5 of the naphthyl); 7.10 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.15 (d, J = 8 Hz, 1H: H4 of the naphthyl); 7.41 (t, J = 8 Hz, 1H: H3 of the naphthyl); 7.56 (d large, J = 9 Hz, 1H: H8 of the naphthyl); 7.66 (mf, 1H: CONH); 7.70 (d, J = 8 Hz, 1H: H2 of the naphthyl).

- ultimate analysis: $C_{21}H_{27}N_5O_3S$, 1.7 CF_3CO_2H

  Calculated (%): C = 47.01; H = 4.64; N = 11.23; S = 5.14

  Found (%): C = 47.16; H = 4.07; N = 11.33; S = 4.89

EXAMPLE 13: preparation of 4-[6- (3-pyridyl-methylamino)-1-naphthyl-carbonyl] -3(S)-(2-methylthio-ethyl)-2-oxo-piperazine

By proceeding as in example 6 for the preparation of 3(S)-butyl-4-{6-[1-(4-cyanobenzyl)-1H-imidazol-5-yl-methylamino]-1-naphthyl-carbonyl}-2-oxo-piperazine, but using 0.05 g (0.15 mmole) of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine and 0.031 g (0.29 mmole) of 3-pyridine-carboxaldehyde, 0.025 g of trifluoroacetate of 4-[6-(3-pyridyl-methylamino) -1 -naphthyl-carbonyl] -3 (S) - (2-methylthio-ethyl) -2-oxo-piperazine is obtained in the form of a pale yellow freeze-dried product for which the characteristics are as follows:

- DCI mass spectrum (NH_3): M/Z = 435 $(M+H)^+$

-magnetic nuclear resonance spectrum of the proton (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 383 K, δ in ppm): from 1.90 to 2.30 (mt, 2H: CH_2 of the methyl-thio-ethyl); 2.07 (mf, 3H: SCH_3); from 2.50 to 2.75 (mt, 2H: CH_2S); from 3.00 to 3.45 (mt: the H corresponding to the $CONCH_2CH_2NCO$); from 4.20 to 5.00 (mf: 1H corresponding to the NCHCO); 4.51 (s, 2H: NCH_2Ar); 6.90 (d, J = 2.5 Hz, 1H: H5 of the naphthyl); 7.09 (d, J = 7.5 Hz, 1H: H4 of the naphthyl); 7.15 (dd, J = 8.5 and 2.5 Hz, 1H: H7 of the naphthyl); 7.35 (dd, J = 8 and 7.5 Hz, 1H: H3 of the naphthyl); 7.48 (dd, J = 8 and 5 Hz, 1H: H5 of the pyridyl); 7.53 (d, J = 8.5 Hz, 1H: H8 of the naphthyl); from 7.60 to 7.70 (mt, 1H: CONH); 7.63 (d, J = 8 Hz, 1H: H2 of the naphthyl); 7.97 (dt, J = 8 and 1.5 Hz, 1H: H4 of the pyridyl); 8.54 (dd, J = 5 and 1.5 Hz, 1H: H6 of the pyridyl); 8.72 (d, J = 1.5 Hz, 1H:H2 of the pyridyl).

- ultimate analysis: $C_{24}H_{26}N_4O_2S$, 1.5 CF_3CO_2H

Calculated (%): C =53.24; H = 4.54; N = 9.17; S = 5.25

Found (%): C = 53.33; H =4.92; N = 9.59; S = 5.15

EXAMPLE 14: preparation of 4-{6-[1-(4-cyanobenzyl)-1H-imidazol-5-yl-methylamino]-1-naphthyl-carbonyl}-]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine

By proceeding as in example 6 for the preparation of 3(S)-butyl-4-{6-[1-(4-cyanobenzyl)-1H-imidazol-5-yl-methylamino]-1-naphthyl-carbonyl}-2-oxo-piperazine, but using 0.06 g (0.17 mmole) of 4-(6-amino-1-naphthyl-carbonyl)-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine and 0.052 g (0.21 mmole) of 1-(4-cyanobenzyl)-1H-imidazol-5-yl-carboxaldehyde, 0.021 g of trifluoroacetate of 4- {6- [1 - (4-cyanobenzyl) -5 -imidazolyl-methylamino] -1 -naphthyl-carbonyl} -] -3 (S) -(2-methylthio-ethyl)-2-oxo-piperazine is obtained in the form of a white freeze-dried product for which the characteristics are as follows:

- DCI mass spectrum DCI (NH_3): M/Z = 539 $(M+H)^+$

-magnetic nuclear resonance spectrum of the proton (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 393 K, δ in ppm): from 2.05 to 2.30 (mt, 2H: CH_2 of the methyl-sulfanyl-ethyl); 2.08 (s large, 3H: SCH_3); from 2.55 to 2.75 (mt, 2H: CH_2S); from 3.10 to 3.45 and from 3.55 to 3.90 (respectively mt and mf spread, 4H completely: $CONCH_2CH_2NCO$); 4.38 (s, 2H: CH_2Nnaphthyl); from 4.60 to 4.85 (mf spread, 1H: NCHCO); 5.55 (s, 2H: NCH_2Ar); 6.85 (d, J = 2 Hz, 1H: H5 of the naphthyl); 7.03 (dd, J = 9 and 2 Hz, 1H: H7 of the naphthyl); 7.12 (d, J = 7.5 Hz, 1H: H4 of the naphthyl); 7.36 (s large, 1H: N-CH=C of the imidazolyl); 7.38 (dd, J = 8 and 7.5 Hz, 1H: H3 of the naphthyl); from 7.40 to 7.50 (mt, 1H: CONH); 7.43 (d, J = 8 Hz, 2H: H2 and H6 of the 4-cyano-phenyl); 7.53 (d, J = 9 Hz, 1H: H8 of the naphthyl); 7.63 (d, J = 8 Hz, 1H: H2 of the naphthyl); 7.78 (d, J = 8 Hz, 2H: H3 and H5 of the 4-cyano-phenyl); 8.41 (s large, 1H: N=CH-N of the imidazolyl).

- ultimate analysis: $C_{30}H_{30}N_6O_2S$, 1.9 CF_3CO_2H

Calculated (%): C = 53.75; H = 4.26; N = 11.13; S = 4.25

Found (%): C = 53.5; H = 4.68; N = 11.07; S = 4.05

EXAMPLE 15

Evaluation of farnesyl transferase activity of compounds according to the invention

Farnesyl transferase activity is measured by the farnesyled quantity of K-ras substrate or peptide-derived substrate corresponding to its C-terminal part, with the farnesyl group brought by the farnesyl pyrophosphate (FPP).

Precisely, the biotinylated substrate that is used, representative of K-ras: BIOT-$(\beta A)_3$-S-K-D-G-$(K)_6$-S-K-T-K-C-V-I-M, is [^{3}H] farnesyled on its cysteine C, by the farnesyl transferase in the presence of [^{3}H]FPP. It is then put into contact with PVT*-streptavidine (AMERSHAM)® beads, and is quantified by proximity scintillation (dosage SPA) between the tritium and the PVT beads, thanks to the streptavidine/biotin interaction.

Experimentally, farnesyl transferase purified according to the attached protocol, is diluted for this dosage to a concentration such that a substrate consumption of less than 30% is obtained. The final molar concentrations of each substrate are adjusted to their respective Km: 50 nM for the biotinylated K ras peptide and 120 nM for the FPP, made up to 20 µl in a final volume of 100 µl of the reaction mixture of buffer base HEPES 50 mM pH 7.5. $MgCl_2$ 5 mM, KC1 40 mM, dithiothreitol 5 mM, Triton X100 0.01%.

The inhibitors to be tested, initially dissolved in 1 mM in an adequate solvent (DMF or DMSO) are diluted in the assay buffer and are added in the form of 10 µl, in triplicate, into the reaction mixture at a concentration 10 times greater than their final concentration.

The reaction, carried out in with OPTIPLATES 96® checkerboard titration, is initiated by the enzyme and lasts sixty minutes at 37°C. It is stopped by adding 150 µl of a pH 4 stop buffer mixture made up of H_3PO_4 0.2 M, $MgCl_2$ 1.5 mM, BSA 0.5% (p/v), sodium azide 0.05% (p/v) containing 200 µg of PVT-streptavidine beads.

After thirty minutes of slow stirring (in order to eliminate chemiluminescence), the panels are read in [^{3}H]CPM in a TOP COUNT® (PACKARD) scintillation counter for panels where they are transformed into [^{3}H]DPM using a range of coloured agents that reduce scintillation (« quenching »).

The inhibition percentages are calculated in relation to a control group without inhibitor after subtraction of all the values of that of a blank containing only the substrates and the buffer.

The CI_{50} are calculated or measured using inhibitions obtained with nine different concentrations with the Enzfitter® or Grafit® software. The products according to the invention have CI_{50} between 0.1 nM and 100 µM.

EXAMPLE 16

The activity of the compounds according to the invention can also be evaluated by the capacity of said compounds to inhibit the growth in agar of clones stemming from human tumoral lines. For example, cells from the line of human colic carcinoma HCT116, provided by the ATCC, are set to grow as a monolayer in a culture medium, Dubelcco's modified Eagle's medium, containing 2 mM of L-glutamine, 200 U/ml of penicillin, 200 µg/ml of streptomycin supplemented by 10% in volume of heat-inactivated foetal calf serum. Cells in exponential growth are trypsinised, washed with PBS and diluted to a final concentration of 5000 cells/ml in a complete culture medium. The inhibitors to be tested, or the control solvent are then added, in a volume of 50 µl, at 2.5 ml a suspension of cells, previously prepared, then 0.4 ml of an agar solution is added, Noble Difco, maintained at 45°C then it is mixed. The medium thus obtained is immediately placed in Petri dishes, maintained five minutes at 4°C then left to incubate at 37°C in an atmosphere of 5% CO_2. The number of cell clones (> 50 cells) is counted after twelve days of incubation at 37°C in an atmosphere of 5% CO_2. Each inhibitor is tested as duplicates at the final agar concentrations of 10, 1, 0.1, 0.01 and 0.001 (µg/ml. The results are expressed as a percentage of inhibition of clonogenicity in relation to untreated controls. The IC_{50} inhibiting doses are determined graphically using semi-logarithmic averages of the values obtained for each concentration.

The products according to the invention inhibit 50% of the formation of clones at concentrations between 0.1 nM and 100µM.

EXAMPLE 17

EXAMPLE A

According to the normal technique, capsules dosed at 50 mg of active ingredient are prepared with the following composition:

- Active ingredient ..... 50 mg
- Cellulose ..... 18 mg
- Lactose ..... 55 mg
- Colloidal silica ..... 1 mg
- Sodium carboxymethylamidon ..... 10 mg
- Talc ..... 10 mg
- Magnesium stearate ..... 1 mg

EXAMPLE B

According to the normal technique, caplets dosed at 50 mg of active ingredient are prepared with the following composition:

- Active ingredient ..... 50 mg
- Lactose ..... 104 mg
- Cellulose ..... 40 mg
- -Polyvidone ..... 10 mg
- - Sodium carboxymethylamidon ..... 22 mg
- -Talc ..... 10 mg
- Magnesium stearate ..... 2 mg
- Colloidal silica ..... 2 mg
- Mixture of hydroxymethylcellulose, glycerine, titanium dioxide (72-3.5-24.5) q.s.p. 1 film caplet finished at 245..... mg

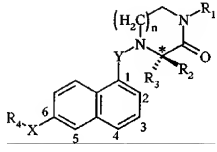
EXAMPLE C

An injectable solution containing 50 mg of active ingredient is prepared with the following composition:

- Active ingredient	50 mg
- Benzoic acid	80 mg
- Benzyl alcohol	0.06 ml
- Sodium benzoate	80 mg
-95% ethyl alcohol	0.4 ml
- Sodium hydroxide	24 mg
- Propyleneglycol	1.6 ml
- Water q.s.p.	4 ml

CLAIMS

1 – Compounds of general formula (I)



(I)

where

R_1 represents an atom of hydrogen or an alkyl radical, or an aralkyl radical; R_2, R_3, identical or different, represent independently an atom of hydrogen or a radical chosen from among the alkyl, aryl, alkylthioalkyl, alkylsulfonylalkyl, carbamoylalkyl, alkoxyalkyl, hydroxyalkyl, aralkyl radicals of which the aryl portion may be substituted by an atom of halogen;

R4 represents

$-CO-CH(NH_2)-CH_2SH$, or

$-CH_2-CH(NH_2)-CH_2SH$,

or

radicals of formula

X represents either an atom of nitrogen substituted by an R_5 radical, or an atom of oxygen;

R_5 represents an atom of hydrogen or an alkyl, aralkyl, heterocycloalkyl radical; Y represents a sulfonyl or carbonyl radical;

n is equal to 1 or 2;

Ri_1 represents a heterocyclyl radical possibly substituted on one or more of the atoms or hetero atoms that it is composed of, by one or several atoms or radicals chosen from among the atoms of halogen or the alkyl, alkoxy, alkyl, aralkyl, aryl radicals, of which the aryl portions or radicals may themselves be substituted by one or several atoms or radicals, chosen from among the atoms of halogen and/or the alkoxy, cyano, nitro, amino, alkylthio, alkylsulfonyl, polyfluoroalkyl, polyfluoroalkoxy radicals,
Ri_2 represents an atom of hydrogen, or a radical chosen from among alkyl, aryl or aralkyl,
in racemic form or of their stereoisomers, as well as in the form of salts.

2 – Compounds according to claim 1 in which:
R_1 represents an atom of hydrogen.

3- Compounds as claimed in any of the previous claims in which: either R_2 and R_3 each represent an alkyl radical, or one of the substituents R_2 or R_3 represents an atom of hydrogen, and the other of the substituents R_2 or R_3 represents an alkyl, alkylthioalkyl, alkoxyalkyl, aralkyl, hydroxyalkyl radical.

4 - Compounds as claimed in any of the previous claims in which:
R_4 represents a $-CH_2-CH(NH_2)-CH_2SH$ radical, or a radical

in which Ri_1 represents a heterocyclyl radical, possibly substituted by one or several atoms or radicals chosen from among the alkyl, aralkyl radicals, of which the aryl part may be substituted by a cyano radical;

Ri_2 represents an atom of hydrogen.

5 - Compounds as claimed in any of the previous claims in which:
X represents a -NH- radical.

6 - Compounds as claimed in any of the previous claims in which:
Y represents a carbonyl radical.

7 - Compounds as claimed in any of the previous claims in which: n is equal to 1.

8 - Compounds as claimed in any of the previous claims in which:

R_4 represents a radical 

in which Ri_1 represents a heterocyclyl radical, possibly substituted by one or several atoms or radicals chosen from among the alkyl, aralkyl radicals, of which the aryl part may be substituted by a cyano radical;
Ri_2 represents an atom of hydrogen.

9 - Compounds as claimed in any of the previous claims in which: R_4 represents a radical

in which Ri_1 represents a imidazolyl radical, possibly substituted by a benzyl radical, of which the aryl part may be substituted by a cyano radical;

Ri_2 represents an atom of hydrogen.

10 – Compound of general formula (I) characterised in that it concerns a compound selected individually from among:
4- [6- (2 (R)- amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl]-3 (S) - (2-methylthio-ethyl)-2-oxo-piperazine
4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-benzyl-2-oxo-piperazine
4- [6- (2 (R) -amino- 3-mercapto-propylamino) - 1-naphthyl-carbonyl] -3 (S) -hydroxymethyl-2-oxo-piperazine
4- [6- (2 (R) -amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -3 (S) -butyl-2-oxo-piperazine

4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(R,S)-methoxymethyl-2-oxo-piperazine

3 (S) -butyl-4- {6- [1 - (4-cyanobenzyl) - 1H-imidazol-5-yl-methylamino] -1 -naphthyl-carbonyl} -2-oxo-piperazine

4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-3(S)-methyl-2-oxo-piperazine

4-[6-(2(R)-amino-3-mercapto-propylamino)-1-naphthyl-carbonyl]-2-oxo-piperazine

4- [6- (2 (R) -amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -1 -methyl-3 (S) -methylthioethyl-2-oxo-piperazine

4- [6- (2 (R) -amino-3-mercapto-propylamino) -1 -naphthyl-carbonyl] -1 -benzyl-3 (S) -methylthioethyl-2-oxo-piperazine

4- [6- (1 -methyl-1H-imidazol- 5-yl-methylamino) -1 -naphthyl-carbonyl] -3 (S) - (2-methylthio-ethyl) -2-oxo-piperazine

3 (S) - (2-carbamoyl-ethyl) -4- [6- (2 (R)-amino-3 -mercapto-propylamino) -1 -naphthyl-carbonyl]-2-oxo-piperazine

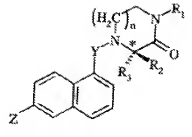
4- [6- (3-pyridyl-methylamino) - 1-naphthyl-carbonyl] -3 (S) - (2-methylthio-ethyl) -2-oxo-piperazine

4-{6-[1-(4-cyanobenzyl)-1H-imidazol-5-yl-methylamino]-1-naphthyl-carbonyl}-]-3(S)-(2-methylthio-ethyl)-2-oxo-piperazine

4- {6- [1 - (4-cyanobenzyl) - 1H-imidazol-5-yl-methylamino] -1 -naphthyl-carbonyl} -] -3 (S) -hydroxymethyl-2-oxo-piperazine

or their stereoisomers, possibly in racemic form as well as their salts.

11 - Method of preparation of compounds of general formula (I) as claimed in any of the preceding claims in which R_1, R_2, R_3, Y and n are defined as such in general formula (I), X represents an atom of nitrogen substituted by R_5 with R_5 representing an atom of hydrogen and when R_4 represents the radical $-CO-CH(NH_2)-CH_2SH$, characterised in that one proceeds using compounds of general formula (II)



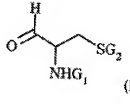
(II)

where R_1, R_2, R_3, Y and n are defined as previously and Z represents an amino radical, by action of a protected amino acid of general formula

$$HO_2C\text{-}CH(NHG_1)\text{-}CH_2SG_2 \qquad (III)$$

where G_1 represents a protective group of an amino function and G_2 represents a protective group of mercapto function, then the protective groups of the amino and mercapto groups are eliminated.

12 - Method of preparation of compounds of general formula (I) as claimed in any of claims 1 to 10 in which R_1, R_2, R_3, Y and n are defined as such in general formula (I), X represents an atom of nitrogen substituted by R_5 with R_5= H and R_4 represents radical -CH_2-$CH(NH_2)$-SH, characterised in that one proceeds using compounds of general formula (II) where R_1, R_2, R_3, Y and n are such as defined as previously and Z represents an amino radical, by action of a reagent of general formula



(IV)

where G_1 and G_2 are defined as previously, then the protective groups of the amino and mercapto radicals are eliminated.

13 - Method of preparation of compounds of general formula (I) as claimed in any of claims 1 to 10 in which R_1, R_2, R_3, Y and n are defined as such in general formula (I), X represents an atom of nitrogen substituted by R_5 with R_5=H and R_4 represents a radical of formula

in which Ri_1 and Ri_2 are such as defined in general formula (I), characterised in that one proceeds using compounds of general formula (II) where R_1, R_2, R_3, Y and n are such as defined as previously and Z represents an amino radical by action of a reagent of general formula

(V)

in which Ri_1 and Ri_2 are defined as previously.

14 - Method of preparation of compounds of general formula (I) as claimed in any of claims 1 to 10 in which R_1, R_2, R_3, Y and n are defined as such in general formula (I), X represents an atom of nitrogen substituted by R_5 representing an alkyl, aralkyl or heterocycloalkyl radical, characterised in that one proceeds using compounds of general formula (I) in which X represents an atom of nitrogen substituted by H, by alkylation with R_5-Hal, where R_5 represents an alkyl, aralkyl or heterocycloalkyl radical, and Hal represents an atom of halogen.

15 - Method of preparation as claimed in any of claims 11 or 12, characterised in that G_1 represents a benzyloxycarbonyl, tert.butoxycarbonyl or vinyloxycarbonyl radical, and G_2 represents a protective group of mercapto function such as trithyl (-CPh_3).

16 - Method of preparation according to claim 11, characterised in that the reaction of the compound of general formula (III) on the compound of general formula (II) is carried out in the presence of 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium, hexafluorophosphate (HBTU), N-hydroxybenzotriazole (HOBT) and diisopropylethylamine in an organic solvent.

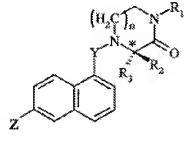
17 - Method of preparation according to claim 12 or 13, characterised in that the reaction of the compound of general formula (IV) on the compound of general formula (II) or the reaction of the product of general formula (V) on the product of general formula (II) is carried out under conditions of reductive amination.

18 - Method of preparation as claimed in one of claims 12, 13 or 17, characterised in that the reaction of the compound of general formula (IV) on the compound of general formula (II) or the reaction of the product of general formula (V) on the product of general formula (II) is carried out by working in an organic solvent, in the presence of acid, then by the action of a reducing compound.

19 - Method of preparation as claimed in one of claims 12, 13, 17 or 18, characterised in that the reducing compound is sodium cyanoborohydride ($NaBH_3CN$) or sodium triacetoxyborohydride ($NaBH(OCOCH_3)_3$) or the BH_3.pyridine complex.

20 - Method of preparation according to claim 14, characterised in that the reaction of alkylation is carried out by working in the presence of a mineral base such as potassium carbonate, in an organic solvent such as acetonitrile.

21 - Method of preparation of compounds of general formula (I) as claimed in any of claims 1 to 10, in which R_2, R_3, R_4, Y and n are defined as such in general formula (I), X represents an atom of oxygen and R_1 represents an atom of hydrogen or an alkyl or aralkyl radical, characterised in that one proceeds using corresponding compounds of general formula (II)



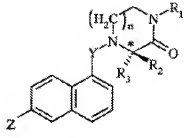
(II)

where R_2, R_3, Y and n are defined as such in general formula (I), Z represents an $-OR_4$ radical, R_4 being defined as in general formula (I) and R_1 represents an

atom of hydrogen, by action of a base, followed possibly by the reaction of alkylation of the atom of nitrogen with R1-Hal, where R_1 represents an alkyl or aralkyl radical.

22 - Method of preparation according to claim 21, characterised in that the base is an alkaline metal hydride, such as sodium hydride.

23 – Compounds of general formula (II)



(II)

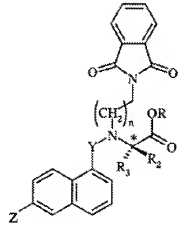
where R_1, R_2, R_3, Y and n are defined as such in general formula (I) and Z represents a nitro, amino, possibly protected, radical or $-OR_4$ with R_4 defined as in general formula (I).

24 - Method of preparation of compounds of general formula (II) according to claim 23 where R_1, R_2, R_3, Y and n are defined as such in general formula (I), Z represents an amino radical, characterised in that the corresponding products of general formula (II) are reduced where R_1, R_2, R_3, Y and n are defined as such in general formula (I) and Z represents a nitro radical, in an organic solvent.

25 - Method of preparation according to claim 24 characterised in that the catalytic reduction is carried out in a hydrogen atmosphere using Palladium on carbon, or using tin tetrachloride.

26 - Method of preparation of compounds of general formula (II) according to claim 23 where R_1, R_2, R_3 and n are defined as such in general formula (I), Z represents an amino radical, and Y represents an $-SO_2$ radical, characterised in that the corresponding products of general formula (II) are deprotected where R_1, R_2, R_3, and n are defined as such in general formula (I) and Y represents an-SO_2 radical and Z represents a protected amino radical -NHG, G representing a protective group of the amino function.

27 - Method of preparation of compounds of general formula (II) according to claim 23, where R_2, R_3,Y and n are defined as such in general formula (I), Z represents an -OR_4 radical with R_4 defined as in general formula (I), or a nitro radical, or a protected amino radical and R_1 represents an atom of hydrogen, characterised in that one proceeds using compounds of general formula (VI)



(VI)

where R_2, R_3, Y and n are such as defined as previously, Z represents an -OR_4 radical or a nitro radical or a protected amino radical and R represents an alkyl radical, such as methyl, by the action of an amino base, by working in an organic solvent.

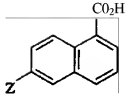
28 – Method according to claim 27, characterised in that the amino base is hydrazine.

29 - Method of preparation according to claim 27, characterised in that the compounds of general formula (VI) implemented where R_1, R_2, R_3, Y, R and n are such as defined in claim 24, and Z represents an -OR_4 radical, R_4 being

defined as in general formula (I), are obtained using products of general formula (VI) where R_2, R_3, Y, R and n are such as defined as previously, and Z represents an -OH radical through exchange reaction of the atom of hydrogen with an $-R_4$ radical, using compounds of general formula Hal-R_4, where R_4 is defined as previously and Hal represents an atom of halogen.

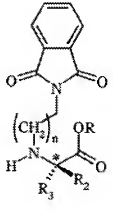
30 – Method according to claim 29 characterised in that one works in the presence of a mineral base.

31 - Method of preparation according to claim 27, characterised in that the compounds of general formula (VI) implemented where R_2, R_3, R and n are such as defined as previously, Y represents a carbonyl radical and Z represents an -OH radical or a nitro radical are obtained using compounds of general formula (VII)



(VII)

where Z is defined as previously, through the action of compounds of general formula (VIII)

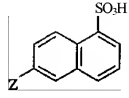


(VIII)

where R, R_2, R_3 and n are defined as previously.

32 - Method of preparation according to claim 31, characterised in that an activated form of acids of general formula (VII) is used.

33 - Method of preparation according to claim 27, characterised in that the compounds of general formula (VI) implemented where R_2, R_3, R and n are such as defined as previously, Y represents a sulfonyl radical and Z represents a nitro or protected amino radical are obtained using compounds of general formula (XII)



(XII)

where Z is defined as previously, by action of compounds of general formula (VIII) where R, R_2, R_3 and n are defined as previously.

34 - Method according to claim 33 characterised in that an activated form of acids of general formula (XII) is used.

35 – Pharmaceutical composition containing at least one product of general formula (I) in association with one or more pharmaceutically acceptable diluents or additives, whether inert or biologically active.

36 - Use of compounds of general formula (I) for the preparation of pharmaceutical compositions useful in the treatment and/or prevention of pathological conditions pertaining to cellular signalling pathways, associated with farnesyl transferase, or with their consequences or symptoms.

37 - Use of compounds of general formula (I) according to the invention for the preparation of pharmaceutical compositions useful in inhibiting farnesyl transferase.

38 - Use of compounds of general formula (I) according to the invention for the preparation of pharmaceutical compositions useful for the treatment of diseases pertaining to cellular proliferation.

39 - Use of compounds of general formula (I) according to the invention for the preparation of pharmaceutical compositions useful for the treatment of cancer.

40 - Association of a product of general formula (I) with one or more pharmacologically active and compatible compounds and/or radiotherapy treatment.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/FR 99/00299

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D241/08 C07D403/12 C07D401/12 A61K31/495

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	WO 96 30343 A (MERCK) 3 October 1996 see claims; tables 1-3	1,23, 35-39

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents:

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"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search

11 May 1999

Date of mailing of the international search report

21/05/1999

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Authorized officer

Francois, J

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/FR 99/00299

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9630343	03-10-1996	US	5856326	05-01-1999
		AU	5322396	16-10-1996
		BG	101973	29-05-1998
		BR	9607953	14-07-1998
		CA	2216707	03-10-1996
		CN	1195340	07-10-1998
		CZ	9703062	18-03-1998
		EP	0820445	28-01-1998
		HR	960143	30-04-1998
		JP	10511098	27-10-1998
		NO	974457	28-11-1997
		NZ	305254	29-03-1999
		PL	322549	02-02-1998
		SK	129297	06-05-1999
		ZA	9602433	02-10-1996

RAPPORT DE RECHERCHE INTERNATIONALE

Dem Internationale No
PCT/FR 99/00299

A. CLASSEMENT DE L'OBJET DE LA DEMANDE
CIB 6 C07D241/08 C07D403/12 C07D401/12 A61K31/495

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

B. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE
Documentation minimale consultée (système de classification suivi des symboles de classement)
CIB 6 C07D A61K

Documentation consultée autre que la documentation minimale dans la mesure où ces documents relèvent des domaines sur lesquels a porté la recherche

Base de données électronique consultée au cours de la recherche internationale (nom de la base de données, et si réalisable, termes de recherche utilisés)

C. DOCUMENTS CONSIDERES COMME PERTINENTS

Catégorie °	Identification des documents cités, avec, le cas échéant, l'indication des passages pertinents	no. des revendications visées
	WO 96 30343 A (MERCK) 3 octobre 1996 voir revendications; tableaux 1-3	1,23, 35-39

I I Voir la suite du cadre C pour la fin de la liste des documents

| | Les documents de familles de brevets sont indiqués en annexe

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Date à laquelle la recherche internationale a été effectivement achevée

11 mai 1999

Date d'expédition du présent rapport de recherche internationale

21/05/1999

Nom et adresse postale de l'administration chargée de la recherche internationale
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Fonctionnaire autorisé

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RAPPORT DE RECHERCHE INTERNATIONALE

Renseignements relatifs aux membres de familles de brevets

Internationale No
Dem PCT/FR 99/00299

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)		Date de publication
WO 9630343	03-10-1996	US	5856326 A	05-01-1999
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